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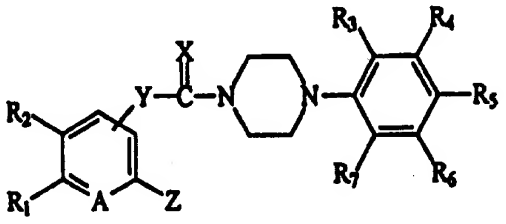
(54) Title: PIPERAZINE DERIVATIVES AND PROCESS FOR THE PREPARATION THEREOF

(57) Abstract



(I)

The present invention relates to novel compound having strong antitumor activities of general formula (I), wherein R_1 and R_2 are independently hydrogen, substituted or unsubstituted C_1-C_8 alkyl, substituted or unsubstituted C_3-C_6 cycloalkyl, substituted or unsubstituted C_2-C_8 unsaturated alkyl, ketone, substituted or unsubstituted aryl, substituted or unsubstituted C_1-C_4 alkoxy, substituted or unsubstituted arylhydroxy, substituted or unsubstituted amino, C_1-C_4 lower ester, C_1-C_4 lower thioester, thiol, substituted or unsubstituted carboxyl, epoxy, substituted or unsubstituted C_1-C_4 lower thioalkoxy; or R_1 and R_2 are fused to form C_3-C_4 saturated or unsaturated chain; R_3, R_4, R_5, R_6 and R_7 are independently hydrogen, halogen, hydroxy, nitro, C_1-C_4 lower ester, C_1-C_4 lower alkyl, C_1-C_4 lower thioalkyl, substituted or unsubstituted C_3-C_6 cycloalkyl, C_1-C_4 lower alkoxy, C_1-C_4 lower thioalkoxy, substituted or unsubstituted aryl, substituted or unsubstituted lower arylalkoxy, substituted or unsubstituted lower alkylamino, or lower alkyl substituted or unsubstituted carbamate; or among R_3, R_4, R_5, R_6 and R_7, two adjacent groups are bonded with each other to form 1,2-phenylene or 2,3-naphthylene; X is oxygen, sulfur, or substituted or unsubstituted imino; Y is bonded at the 3-position or 4-position of the aromatic ring part wherein Y is oxygen or -NR_8- (wherein, R_8 is the same with the above-mentioned R_3); Z is hydroxy, C_1-C_4 lower alkoxy, C_1-C_4 lower thioalkoxy, substituted or unsubstituted aryl xy, C_1-C_4 lower alkylamino, substituted or unsubstituted cycloamino containing 1-5 nitrogen atoms; A is nitrogen or -CH=; its pharmaceutically acceptable acid addition salts and process for the preparation thereof.

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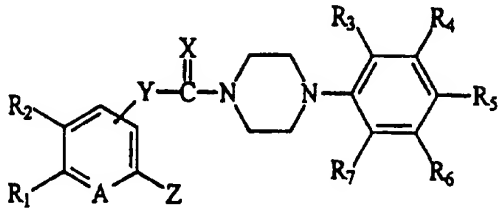
Piperazine derivatives and process for the preparation thereof

The present invention relates to new piperazine derivatives of the general formula (I)



(I)

wherein R_1 and R_2 are independently hydrogen, substituted or unsubstituted C_1-C_8 alkyl, substituted or unsubstituted C_3-C_6 cycloalkyl, substituted or unsubstituted C_2-C_8 unsaturated alkyl, ketone, substituted or unsubstituted aryl, substituted or unsubstituted C_1-C_4 alkoxy, substituted or unsubstituted arylhydroxy, substituted or unsubstituted amino, C_1-C_4 lower ester, C_1-C_4 lower thioester, thiol, substituted or unsubstituted carboxyl, epoxy, substituted or unsubstituted C_1-C_4 lower thioalkoxy; or R_1 and R_2 are fused to form C_3-C_4 saturated or unsaturated chain; R_3, R_4, R_5, R_6 and R_7 are independently hydrogen, halogen, hydroxy, nitro, C_1-C_4 lower ester, C_1-C_4 lower alkyl, C_1-C_4 lower thioalkyl, substituted or unsubstituted C_3-C_6 cycloalkyl, C_1-C_4 lower alkoxy, C_1-C_4 lower thioalkoxy, substituted or unsubstituted aryl, substituted or unsubstituted lower arylalkoxy, substituted or unsubstituted lower alkylamino, or lower alkyl substituted or unsubstituted carbamate; or among R_3, R_4, R_5, R_6 and R_7, two adjacent groups are bonded with each other to form 1,2-phenylene or 2,3-naphthylene; X is oxygen, sulfur, or substituted or unsubstituted imino; Y is bonded at the 3-position or 4-position of the aromatic ring part wherein Y is oxygen or $-NR_8-$ (wherein, R_8 is the same with the above-mentioned R_3.); Z is hydroxy, C_1-C_4 lower alkoxy, C_1-C_4 lower thioalkoxy, substituted or unsubstituted aryloxy, C_1-C_4 lower alkylamino, substituted or unsubstituted cycloamino containing 1-5 nitrogen atoms; A is nitrogen or -CH=; its pharmaceutically acceptable acid addition

salts and process for the preparation thereof.

In the above definitions, C_1-C_8 alkyl means straight or branched alkyl group such as methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl, iso-pentyl, hexyl, heptyl, octyl, 2-methylpentyl or the like.

C_1-C_4 lower alkyl means methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl or tert-butyl.

Substituted or unsubstituted C_3-C_6 cycloalkyl means substituted or unsubstituted cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, substituted cyclopropyl, substituted cyclopentyl, substituted cyclohexyl or the like.

C_1-C_4 lower ester means a carboxyl group esterified by a lower alkyl group.

C_1-C_4 lower alkoxy means methoxy, ethoxy, propoxy, isopropoxy, butyloxy, isobutyloxy, tert-butyloxy group or the like.

C_1-C_4 lower thioalkoxy means methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, tert-butylthio group or the like.

C_1-C_4 lower alkylamino means methylamino, ethylamino, propylamino, butylamino group or the like.

Aryloxy means phenoxy, substituted phenoxy, naphthyloxy or substituted naphthyloxy or the like.

Cycloamino group containing 1-5 nitrogen atoms means pyrrolidinyl, pyrrolinyl, imidazolyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, piperazinyl or the like.

The present inventors had studied for a long time to find compounds having intensive antitumor activity. As the results, now we have finally found out the facts that the present compounds of the general formula(I) and acid addition salts thereof have not only prominent antitumor activities but very low toxicities.

Accordingly, the one object of the present invention is to provide the novel compounds of the general formula(I) and acid addition salts thereof having not only prominent antitumor activities but very low toxicities.

The other object of the present invention is to provide a process for

the preparation of the compounds of general formula(I) and acid addition salts thereof.

The compounds of the present invention can be mixed with pharmaceutically acceptable vehicles by a known method to give pharmaceutical compositions and the pharmaceutical compositions can be used to prevent or treat with various kinds of tumors of human beings or mammals.

Therefore, another object of the present invention is to provide pharmaceutical compositions containing the compounds of the general formula(I) or acid addition salts thereof as active ingredients.

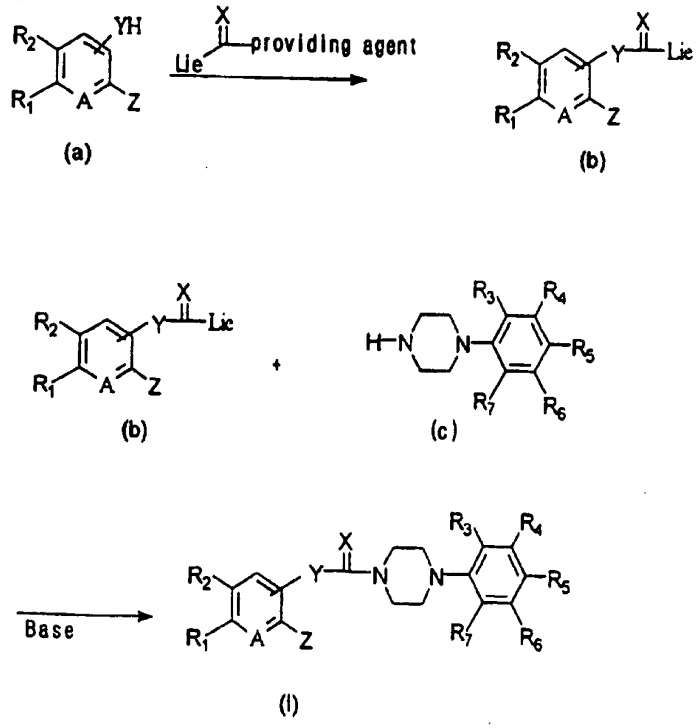
Acids which can be reacted with the compounds of the general formula(I) to form acid addition salts are pharmaceutically acceptable inorganic or organic acids; for example, inorganic acids such as hydrochloric acid, bromic acid, sulfuric acid, phosphoric acid, nitric acid; organic acids such as formic acid, acetic acid, propionic acid, succinic acid, citric acid, maleic acid, malonic acid, glycolic acid, lactic acid; amino acids such as glycine, alanine, valine, leucine, isoleucine, serine, cysteine, cystine, asparaginic acid, glutamic acid, lysine, arginine, tyrosine, proline; sulfonic acids such as methane sulfonic acid, ethane sulfonic acid, benzene sulfonic acid, toluene sulfonic acid; or the like.

Vehicles which can be used in the preparation of pharmaceutical compositions containing the compounds of the general formula(I) as active ingredients are sweetening agent, binding agent, dissolving agent, aids for dissolution, wetting agent, emulsifying agent, isotonic agent, adsorbent, degrading agent, antioxident, antiseptics, lubricating agent, filler, perfume or the like; such as lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycine, silica, talc, stearic acid, stearin, magnesium stearate, calcium stearate, magnesium aluminum silicate, starch, gelatine, tragacanth gum, glycine, silica, alginic acid, sodium alginate, methyl cellulose, sodium carboxy methyl cellulose, agar, water, ethanol, polyethylenglycol, polyvinyl pyrrolidone, sodium chloride, potassium chloride, orange essence, strawberry essence, vanila aroma or the like.

Daily dosage of the compound of the general formula(I) may be varied depending on age, sex of patient and the degree of disease. Daily dosage is 1.0mg to 5,000mg may be administered one to several times.

The compounds of the general formula (I) according to the present invention may be prepared by the following scheme I.

Scheme I



wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, A, X, Y and Z are as defined above, and Lie is a leaving group such as halogen atom, sulfonyl or the like.

The above process comprises reacting a compound of the general formula(a) with a -C(=X)- group-providing agent in organic solvent to obtain a compound of the general formula(b) and successively reacting the compound of the general formula(b) with a compound of the general formula(c) to give the compound of the general formula(I). The used -C(=X)-group-providing agent preferably be selected from 1,1-carbonyldiimidazole, 1,1-carbonylthiodiimidazole, phosgene, thiophosgene, carbonyldiphenoxide, phenylchloroformate or the like. The reaction may be carried out in conventional organic solvent such as, for example, tetrahydrofuran, dichloromethane, chloroform,

acetonitrile.

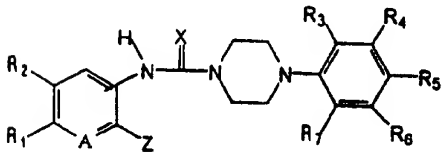
And also the reaction is preferably carried out in the presence of coupling agent such as conventional inorganic or organic base. Such conventional inorganic or organic base used in the reaction means sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium bicarbonate, potassium bicarbonate, triethylamine, pyridine, DBU or the like, and 1-1.5 equivalent, preferably 1-1.1 equivalent thereof may be used.

The reaction may be carried out between 3℃ and boiling point of the solvent used, preferably at 50℃-100℃ for 5 - 48 hours, preferably for 10 - 24 hours.

-C(=X)-group-providing agent may be used in an amount of 1 - 1.5 equivalent, preferably 1-1.1 equivalent to the starting compound.

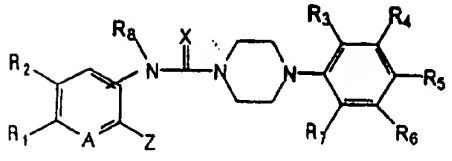
A compound of the general formula(I) wherein Y is $-NR_8-$ may be prepared by the following scheme II

Scheme II.



(Ia)

R_8 providing agent



(Ib)

wherein, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, A, X and Z are as defined above.

A compound of the general formula(Ib) above may be prepared effectively by introducing R_8 providing agent into a compound of the general formula(Ia).

R_8 providing agent preferably used in the above reaction is C_1-C_8 lower alkylhalogen, C_1-C_8 lower alkyl sulfonate, substituted or unsubstituted C_3-C_8 cycloalkylhalogen, arylhalogen, substituted or unsubstituted C_3-C_8 cycloalkyl sulfonate, arylsulfonate, or the like.

C_1-C_8 lower alkylhalogen means methylchloride, methylbromide, methyliodide, ethylchloride, ethylbromide, ethyliodide, propylchloride, propylbromide, propyliodide, butylchloride, butylbromide, butyliodide, pentylchloride, pentylbromide, pentyliodide, ethylbromoacetate, or the like.

C_1-C_8 lower alkyl sulfonate means methylsulfonate, ethylsulfonate, propylsulfonate, butylsulfonate, pentylsulfonate, or the like.

Substituted or unsubstituted C_3-C_8 cycloalkylhalogen cyclopropylchloride, cyclopropylbromide, cyclopropyliodide, cyclobutylchloride, cyclobutylbromide, cyclobutyliodide, cyclopentylchloride, cyclopentylbromide, cyclopentyliodide, cyclohexylchloride, cyclohexylbromide, cyclohexyliodide, cyclopropyl methylchloride, cyclopropyl methylbromide, cyclopropyl methyliodide, cyclobutyl methylchloride, cyclobutyl methylbromide, cyclobutyl methyliodide, cyclopentyl methylchloride, cyclopentyl methylbromide, cyclopentyl methyliodide, cyclohexyl methylchloride, cyclohexyl methylbromide, cyclohexyl methyliodide, or the like.

Arylhalogen means benzylchloride, benzylbromide, benzyliodide, benzoylchloride, benzoylbromide, benzoyliodide, toluylchloride, toluylbromide, toluyliodide, or the like.

Substituted or unsubstituted C_3-C_8 cycloalkyl sulfonate means cyclopropyl sulfonate, cyclobutyl sulfonate, cyclopentyl sulfonate,

cyclohexyl sulfonate, methylcyclopropyl sulfonate, methylcyclobutyl sulfonate, methylcyclopentyl sulfonate, methylcyclohexyl sulfonate, or the like.

Arylsulfonate means benzyl sulfonate, benzoyl sulfonate, toluyl sulfonate, or the like.

More particularly, a compound of the general formula (1a) may be reacted with an alkylating agent or arylating agent in a solvent at the temperature of 25-80℃, for 30 minutes - 20 hours to give the object compound of the general formula(Ib).

An alkylating agent or arylating agent may be used in amount of 1.0 - 1.5 equivalent.

Conventional organic solvent such as for example tetrahydrofuran, dichloromethane, acetonitrile, dimethylformamide may be used in the above reaction.

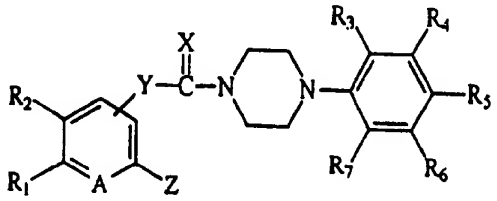
In the above reactions, if any acid material is formed, any basic material may be preferably added as scavenger in order to eliminate the acid material from the reaction phase. Such basic material may be alkali metal hydroxide, alkali earth metal hydroxide, alkali metal oxide, alkali earth metal oxide, alkali metal carbonate, alkali earth metal carbonate, alkali metal hydrogen carbonate, alkali earth metal hydrogen carbonate such as sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, magnesium oxide, calcium oxide, potassium carbonate, sodium carbonate, calcium carbonate, magnesium carbonate, magnesium bicarbonate, sodium bicarbonate, calcium bicarbonate or the like, or organic amines.

The compound of the general formula(a) is described in prior art (J. Med. Chem., 1992, 35, 3784, 3792) or may be prepared in a similar method to the art.

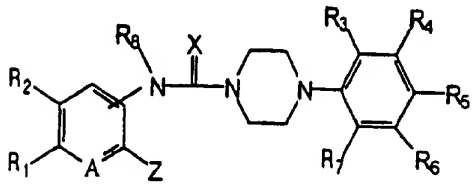
Hereinafter the present invention will be described in more details with reference to following examples but it is not intended to limit the scope

of the invention thereinto.

Compounds of the general formula(I) and formula(Ib) are prepared in following examples according to the above-mentioned process.



(I)



(Ib)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, A, X, Y, Z are the same above.

Ex. No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	A	X	Y	Z	Y
1	Me	Me	SMe	H	H	H	H	N	O	NH	OMe	3-N
2	Me	Me		H	H	H	H	N	O	NH	OMe	3-N
3	Me	Me	Me	Me	H	Me	Me	N	O	NH	OMe	3-N
4	Me	Et	SMe	H	H	H	H	N	O	NH	OMe	3-N
5	Me	Et		H	H	H	H	N	O	NH	OMe	3-N
6	Me	Et	Me	Me	H	Me	Me	N	O	NH	OMe	3-N
7	Me	Et	H	SH	H	H	H	N	O	NH	OMe	3-N
8	Me	nPr	H	OMe	H	OMe	H	N	O	NH	OMe	3-N
9	Me	nPr	H	Me	H	Me	H	N	O	NH	OMe	3-N
10	Me	nPr	H	F	H	F	H	N	O	NH	OMe	3-N
11	Me	nPr	OMe	H	H	H	H	N	O	NH	OMe	3-N
12	Et	Me	H	OMe	H	OMe	H	N	O	NH	OMe	3-N
13	Et	Me	H	Me	H	Me	H	N	O	NH	OMe	3-N
14	Et	Me	H	OH	H	H	H	N	O	NH	OMe	3-N

Ex. No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	A	X	Y	Z	Y
15	nPr	Me	H	OMe	H	OMe	H	N	O	NH	OMe	3-N
16	nPr	Me	H	Me	H	Me	H	N	O	NH	OMe	3-N
17	nPr	Me	H	OH	H	H	H	N	O	NH	OMe	3-N
18	$-(CH_2)_3-$		H	OMe	H	OMe	H	N	O	NH	OMe	3-N
19	$-(CH_2)_3-$		H	Me	H	Me	H	N	O	NH	OMe	3-N
20	$-(CH_2)_4-$		H	OMe	H	OMe	H	N	O	NH	OMe	3-N
21	$-(CH_2)_4-$		H	Me	H	Me	H	N	O	NH	OMe	3-N
22	Me	Me	H	Me	H	Me	H	N	S	NH	OMe	3-N
23	Me	Me	H	F	H	F	H	N	S	NH	OMe	3-N
24	Me	Me	H	OH	H	H	H	N	S	NH	OMe	3-N
25	Me	nPr	H	OMe	H	OMe	H	N	S	NH	OMe	3-N
26	nPr	Me	H	OMe	H	OMe	H	N	S	NH	OMe	3-N
27	nPr	Me	H	Me	H	Me	H	N	S	NH	OMe	3-N
28	nPr	Me	H	OH	H	H	H	N	S	NH	OMe	3-N
29	$-(CH_2)_3-$		H	OMe	H	OMe	H	N	S	NH	OMe	3-N
30	$-(CH_2)_3-$		H	Me	H	Me	H	N	S	NH	OMe	3-N
31	$-(CH_2)_4-$		H	OMe	H	OMe	H	N	S	NH	OMe	3-N
32	$-(CH_2)_4-$		H	Me	H	Me	H	N	S	NH	OMe	3-N
33	Me	Me	H	OMe	H	OMe	H	N	O	NH	NHMe	3-N
34	Me	Me	H	Me	H	Me	H	N	O	NH	NHMe	3-N
35	Me	Et	H	Me	H	Me	H	N	O	NH	NHMe	3-N
36	$-(CH_2)_3-$		H	OMe	H	OMe	H	N	O	NH	NHMe	3-N
37	$-(CH_2)_3-$		H	Me	H	Me	H	N	O	NH	NHMe	3-N
38	Me	Me	H	OMe	H	OMe	H	N	O	NH		3-N
39	Me	Me	H	Me	H	Me	H	N	O	NH		3-N

Ex. No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	A	X	Y	Z	Y
40	Me	Et	H	OMe	H	OMe	H	N	O	NH		3-N
41	Me	Et	H	Me	H	Me	H	N	O	NH		3-N
42	Me	Me	H	OMe	H	OMe	H	N	O	NH		3-N
43	Me	Me	H	Me	H	Me	H	N	O	NH		3-N
44	Me	Et	H	OMe	H	OMe	H	N	O	NH		3-N
45	Me	Et	H	Me	H	Me	H	N	O	NH		3-N
46	Me	Ac	H	OMe	H	OMe	H	N	O	NH	OMe	3-N
47	Me	Ac	H	Me	H	Me	H	N	O	NH	OMe	3-N
48	Me	Ac	H	F	H	F	H	N	O	NH	OMe	3-N
49	Me	Ac	H	Cl	H	Cl	H	N	O	NH	OMe	3-N
50	Me	Ac	Me	Me	H	H	H	N	O	NH	OMe	3-N
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54	Me	Ac	H	Me	H	Me	H	N	S	NH	OMe	3-N
55	Me	Ac	H	OH	H	H	H	N	S	NH	OMe	3-N
56	Me		H	OMe	H	OMe	H	N	O	NH	OMe	3-N
57	Me		H	Me	H	Me	H	N	O	NH	OMe	3-N
58	Me		Me	Me	H	H	H	N	O	NH	OMe	3-N
59	Me		H	F	H	F	H	N	O	NH	OMe	3-N
60	Me		H	Cl	H	Cl	H	N	O	NH	OMe	3-N
61	Me		OMe	H	H	H	H	N	O	NH	OMe	3-N
62	Me		H	OH	H	H	H	N	O	NH	OMe	3-N
63	Me		H	OMe	H	OMe	H	N	S	NH	OMe	3-N
64	Me		H	Me	H	Me	H	N	S	NH	OMe	3-N

Ex. No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	A	X	Y	Z	Y
65	Me		H	OMe	H	OMe	H	N	O	NH	OMe	3-N
66	Me		H	Me	H	Me	H	N	O	NH	OMe	3-N
67	Me		H	OMe	H	OMe	H	N	O	NH	OMe	3-N
68	Me		H	Me	H	Me	H	N	O	NH	OMe	3-N
69	Me		H	OMe	H	OMe	H	N	O	NH	OMe	3-N
70	Me		H	Me	H	Me	H	N	O	NH	OMe	3-N
71	Me		H	OMe	H	OMe	H	N	O	NH	OMe	3-N
72	Me		H	Me	H	Me	H	N	O	NH	OMe	3-N
73	Me	Vinyl	H	OMe	H	OMe	H	N	O	NH	OMe	3-N
74	Me	Vinyl	H	Me	H	Me	H	N	O	NH	OMe	3-N
75	Me	Vinyl	H	F	H	F	H	N	O	NH	OMe	3-N
76	Me		H	OMe	H	OMe	H	N	O	NH	OMe	3-N
77	Me		H	Me	H	Me	H	N	O	NH	OMe	3-N
78	Me		H	OMe	H	OMe	H	N	O	NH	OMe	3-N
79	Me		H	OMe	H	OMe	H	N	O	NH	OMe	3-N
80	Me		H	Me	H	Me	H	N	O	NH	OMe	3-N

Ex. No.	R_1 and R_2	R_3	R_4	R_5	R_6	R_7	R_8	A	X	Z	Y
81	-CH=CH-CH=CH-	H	OMe	H	OMe	H	H	N	O	OMe	3-N
82	-CH=CH-CH=CH-	H	Me	H	Me	H	H	N	O	OMe	3-N
83	-CH=CH-CH=CH-	Me	Me	H	H	H	H	N	O	OMe	3-N
84	-CH=CH-CH=CH-	H	F	H	F	H	H	N	O	OMe	3-N
85	-CH=CH-CH=CH-	H	Cl	H	Cl	H	H	N	O	OMe	3-N
86	-CH=CH-CH=CH-	F	H	H	H	H	H	N	O	OMe	3-N
87	-CH=CH-CH=CH-	Cl	H	H	H	H	H	N	O	OMe	3-N
88	-CH=CH-CH=CH-	H	Cl	H	H	H	H	N	O	OMe	3-N
89	-CH=CH-CH=CH-	H	OH	H	H	H	H	N	O	OMe	3-N
90	-CH=CH-CH=CH-	OMe	H	H	H	H	H	N	O	OMe	3-N
91	-CH=CH-CH=CH-	SMe	H	H	H	H	H	N	O	OMe	3-N
92	-CH=CH-CH=CH-	H		H	H	H	H	N	O	OMe	3-N
93	-CH=CH-CH=CH-	H		H	H	H	H	N	O	OMe	3-N
94	-CH=CH-CH=CH-	OMe	H	H	Me	H	H	N	O	OMe	3-N
95	-CH=CH-CH=CH-	OMe	H	H	Ph	H	H	N	O	OMe	3-N
96	-CH=CH-CH=CH-	Me	H	H	OMe	H	H	N	O	OMe	3-N
97	-CH=CH-CH=CH-	-Benzo-		H	H	H	H	N	O	OMe	3-N
98	-CH=CH-CH=CH-	H	OMe	H	OMe	H	Me	N	O	OMe	3-N
99	-CH=CH-CH=CH-	H	OMe	H	OMe	H	Et	N	O	OMe	3-N
100	-CH=CH-CH=CH-	H	OMe	H	OMe	H	iPr	N	O	OMe	3-N
101	-CH=CH-CH=CH-	H	OMe	H	OMe	H		N	O	OMe	3-N
102	-CH=CH-CH=CH-	H	OMe	H	OMe	H	Benzyl	N	O	OMe	3-N
103	-CH=CH-CH=CH-	H	Me	H	Me	H	Me	N	O	OMe	3-N
104	-CH=CH-CH=CH-	H	Me	H	Me	H	Et	N	O	OMe	3-N
105	-CH=CH-CH=CH-	H	Me	H	Me	H	iPr	N	O	OMe	3-N

Ex. No	R_1 and R_2	R_3	R_4	R_5	R_6	R_7	R_8	A	X	Z	Y
106	-CH=CH-CH=CH-	H	Me	H	Me	H	Benzyl	N	O	OMe	3-N
107	-CH=CH-CH=CH-	H		H	H	H	Me	N	O	OMe	3-N
108	-CH=CH-CH=CH-	H		H	H	H	Et	N	O	OMe	3-N
109	-CH=CH-CH=CH-	H	OMe	H	OMe	H	H	N	S	OMe	3-N
110	-CH=CH-CH=CH-	H	Me	H	Me	H	H	N	S	OMe	3-N
111	-CH=CH-CH=CH-	H	F	H	F	H	H	N	S	OMe	3-N
112	-CH=CH-CH=CH-	H	Cl	H	Cl	H	H	N	S	OMe	3-N
113	-CH=CH-CH=CH-	H	OMe	H	H	H	H	N	S	OMe	3-N
114	-CH=CH-CH=CH-	H	OMe	H	OMe	H	H	N	O	Me	3-N
115	-CH=CH-CH=CH-	H	Me	H	Me	H	H	N	O	Me	3-N
116	-CH=CH-CH=CH-	Me	Me	H	H	H	H	N	O	Me	3-N
117	-CH=CH-CH=CH-	H	F	H	F	H	H	N	O	Me	3-N
118	-CH=CH-CH=CH-	H	Cl	H	Cl	H	H	N	O	Me	3-N
119	-CH=CH-CH=CH-	OMe	H	H	H	H	H	N	O	Me	3-N
120	-CH=CH-CH=CH-	F	H	H	H	H	H	N	O	Me	3-N
121	-CH=CH-CH=CH-	Cl	H	H	H	H	H	N	O	Me	3-N
122	-CH=CH-CH=CH-	SMe	H	H	H	H	H	N	O	Me	3-N
123	-CH=CH-CH=CH-	OMe	H	H	Me	H	H	N	O	Me	3-N
124	-CH=CH-CH=CH-	-Benzo-		H	H	H	H	N	O	Me	3-N
125	-CH=CH-CH=CH-	H	OMe	H	OMe	H	H	N	S	Me	3-N
126	-CH=CH-CH=CH-	H	Me	H	Me	H	H	N	S	Me	3-N
127	-CH=CH-CH=CH-	H	F	H	F	H	H	N	S	Me	3-N
128	-CH=CH-CH=CH-	H	OMe	H	OMe	H	H	N	O	2-Py	4-N
129	-CH=CH-CH=CH-	H	OMe	H	OMe	H	H	N	O	3-Py	4-N
130	-CH=CH-CH=CH-	H	OMe	H	OMe	H	H	N	O	2-Thienyl	4-N
131	-CH=CH-CH=CH-	H	Me	H	Me	H	H	N	O	3-Py	4-N

Ex. No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	A	X	Z	Y
132	Me	Me	H	OMe	H	OMe	H	Me	N	O	OMe	3-N
133	Me	Me	H	OMe	H	OMe	H	Et	N	O	OMe	3-N
134	Me	Me	H	OMe	H	OMe	H	i-Pr	N	O	OMe	3-N
135	Me	Me	H	Me	H	Me	H	Me	N	O	OMe	3-N
136	Me	Me	OMe	H	H	H	H	Me	N	O	OMe	3-N
137	Me	Me	OMe	H	H	H	H	Et	N	O	OMe	3-N
138	Me	Me	OMe	H	H	H	H	Bn	N	O	OMe	3-N
139	Me	Me	OMe	H	H	H	H		N	O	OMe	3-N
140	Me	Me	Me	H	H	OMe	H	Me	N	O	OMe	3-N
141	Me	Me	Me	H	H	OMe	H	Et	N	O	OMe	3-N
142	Me	Me	Me	H	H	OMe	H	Bn	N	O	OMe	3-N
143	Me	Et	H	OMe	H	OMe	H	Me	N	O	OMe	3-N
144	Me	Et	H	Me	H	Me	H	Me	N	O	OMe	3-N
145	Me	Et	H	Me	H	Me	H	Et	N	O	OMe	3-N

Ex. No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	A	X	Z	Y
146	Me	nPr	H	OMe	H	OMe	H	Me	N	O	OMe	3-N
147	Et	Me	H	OMe	H	OMe	H	Me	N	O	OMe	3-N
148	nPr	Me	H	OMe	H	OMe	H	Me	N	O	OMe	3-N
149	Me	Ac	H	OMe	H	OMe	H	Me	N	O	OMe	3-N
150	Me	Ac	H	OMe	H	OMe	H	Et	N	O	OMe	3-N
151	Me	Ac	H	Me	H	Me	H	Me	N	O	OMe	3-N
152	Me		H	OMe	H	OMe	H	Me	N	O	OMe	3-N
153	Me		H	OMe	H	OMe	H	Et	N	O	OMe	3-N
154	Me		H	Me	H	Me	H	Me	N	O	OMe	3-N
155	Me		H	OMe	H	OMe	H	Me	N	O	OMe	3-N
156	Me		H	Me	H	Me	H	Me	N	O	OMe	3-N
157	Me		H	OMe	H	OMe	H	Me	N	O	OMe	3-N
158	Me	Vinyl	H	OMe	H	OMe	H	Me	N	O	OMe	3-N
159	Me	Vinyl	H	Me	H	Me	H	Me	N	O	OMe	3-N
160	Me	Vinyl	H	OMe	H	OMe	H	Et	N	O	OMe	3-N
161	Me		H	OMe	H	OMe	H	Me	N	O	OMe	3-N
162	Me		H	Me	H	Me	H	Me	N	O	OMe	3-N
163	Me	Ac	H	OMe	H	OMe	H		N	O	OMe	3-N
164	Me	Ac	H	Me	H	Me	H		N	O	OMe	3-N
165	Me	Ac	H	OMe	H	OMe	H		N	O	OMe	3-N
166	Me		H	OMe	H	OMe	H		N	O	OMe	3-N
167	Me		H	OMe	H	OMe	H		N	O	OMe	3-N
168	Me		H	Me	H	Me	H		N	O	OMe	3-N
169	Me		H	Me	H	Me	H		N	O	OMe	3-N

Ex. No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	A	X	Z	Y
170	Me	Me	H	H	H	H	H	H	CH	O	OMe	3-N
171	Me	Me	H	OMe	H	OMe	H	H	CH	O	OMe	3-N
172	Me	Me	H	Me	H	Me	H	H	CH	O	OMe	3-N
173	Me	Me	Me	Me	H	H	H	H	CH	O	OMe	3-N
174	Me	Me	Me	Me	H	Me	Me	H	CH	O	OMe	3-N
175	Me	Me	H	F	H	F	H	H	CH	O	OMe	3-N
176	Me	Me	Cl	H	H	H	H	H	CH	O	OMe	3-N
177	Me	Me	H	Cl	H	H	H	H	CH	O	OMe	3-N
178	Me	Me	OH	H	H	H	H	H	CH	O	OMe	3-N
179	Me	Me	H	OH	H	H	H	H	CH	O	OMe	3-N
180	Me	Me	H	SH	H	H	H	H	CH	O	OMe	3-N
181	Me	Me	OAc	H	H	H	H	H	CH	O	OMe	3-N
182	Me	Me	H	OAc	H	H	H	H	CH	O	OMe	3-N
183	Me	Me	OMe	H	H	H	H	H	CH	O	OMe	3-N
184	Me	Me	H	Me	H	H	OMe	H	CH	O	OMe	3-N
185	Me	Me	H	OMe	H	H	Me	H	CH	O	OMe	3-N
186	Me	Me	H	OMe	H	H	Ph	H	CH	O	OMe	3-N
187	Me	Me			H	H	H	H	CH	O	OMe	3-N
188	Me	Me	Benzo		H	H	H	H	CH	O	OMe	3-N
189	Me	Me	Naphto		H	H	H	H	CH	O	OMe	3-N
190	Me	Me	H	OMe	H	OMe	H	Me	CH	O	OMe	3-N
191	Me	Me	H	Me	H	Me	H	Me	CH	O	OMe	3-N
192	Me	Me	H	F	H	F	H	Me	CH	O	OMe	3-N
193	Me	Me	H	OMe	H	OMe	H	Et	CH	O	OMe	3-N
194	Me	Me	H	Me	H	Me	H	Et	CH	O	OMe	3-N

Ex. No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	A	X	Z	Y
195	Me	Me	H	F	H	F	H	Et	CH	O	OMe	3-N
196	Me	Me	H	F	H	F	H	iPr	CH	O	OMe	3-N
197	Me	Me	H	OMe	H	OMe	H	H	CH	S	OMe	3-N
198	Me	Me	H	Me	H	Me	H	H	CH	S	OMe	3-N
199	Me	Me	Me	Me	H	H	H	H	CH	S	OMe	3-N
200	Me	Me	H	F	H	F	H	H	CH	S	OMe	3-N
201	Me	Me	H	Cl	H	Cl	H	H	CH	S	OMe	3-N
202	Me	Me	F	H	H	H	H	H	CH	S	OMe	3-N
203	Me	Me	Cl	H	H	H	H	H	CH	S	OMe	3-N
204	Me	Me	OMe	H	H	H	H	H	CH	S	OMe	3-N
205	Me	Me	SMe	H	H	H	H	H	CH	S	OMe	3-N
206	Me	Me	H	OH	H	H	H	H	CH	S	OMe	3-N
207	Me	Me	OPh	H	H	H	H	H	CH	S	OMe	3-N
208	Me	Me		H	H	H	H	H	CH	S	OMe	3-N
209	Me	Me	H	OMe	H	H	Me	H	CH	S	OMe	3-N
210	Me	Me	Benzo		H	H	H	H	CH	S	OMe	3-N
211	Me	Acetyl	H	OMe	H	OMe	H	H	CH	O	OMe	3-N
212	Me	Acetyl	H	Me	H	Me	H	H	CH	O	OMe	3-N
213	Me	Acetyl	H	Cl	H	Cl	H	H	CH	O	OMe	3-N
214	Me		H	OMe	H	OMe	H	H	CH	O	OMe	3-N
215	Me		H	Me	H	Me	H	H	CH	O	OMe	3-N
216	Me	Vinyl	H	OMe	H	OMe	H	H	CH	O	OMe	3-N
217	Me	Vinyl	H	Me	H	Me	H	H	CH	O	OMe	3-N
218	Me	Acetyl	H	OMe	H	OMe	H	H	CH	S	OMe	3-N
219	Me	Acetyl	H	Me	H	Me	H	H	CH	S	OMe	3-N
220	Me	Acetyl	H	Cl	H	Cl	H	H	CH	S	OMe	3-N
221	Me		H	OMe	H	OMe	H	H	CH	S	OMe	3-N

Ex. No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	A	X	Z	Y
222	Me		H	Me	H	Me	H	H	CH	S	OMe	3-N
223	Me		H	Cl	H	Cl	H	H	CH	S	OMe	3-N
224	Me	Me	H	OMe	H	OMe	H		CH	O	OMe	3-N
225	Me	Me	H	Me	H	Me	H		CH	O	OMe	3-N
226	Me	Me	H	OMe	H	OMe	H		CH	O	OMe	3-N
227	Me	Me	H	Me	H	Me	H		CH	O	OMe	3-N
228	Me	Me	H	OMe	H	OMe	H	H	CH	O	OH	3-N
229	Me	Me	H	Me	H	Me	H	H	CH	O	OH	3-N
230	Me	Me	H	F	H	F	H	H	CH	O	OH	3-N
231	Me	Me	H	Cl	H	Cl	H	H	CH	O	OH	3-N

Example 1

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methylthiophenyl)piperazine:

a) Phenyl N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate:

3-Amino-5,6-dimethyl-2-methoxypyridine(1.52g, 0.01mol) and phenylchloroformate(1.56g, 0.01mol) were dissolved in dichloromethane and was stirred at room temperature for 2 hours. The mixture was concentrated under the reduced pressure to remove the solvent. The concentrate was purified by column chromatography(ethylacetate : hexane = 1:6) to obtain the titled compound.

yield: 92 %

^{1}H-NMR($CDCl_3$) δ : 2.18(3H,s), 2.36(3H,s), 4.00(3H,s), 7.31(5H,m), 8.07(1H,s)

b) 1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methylthiophenyl)piperazine:

Phenyl N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate(136mg, 0.5mmol) and 1-(2-methylthiophenyl)piperazine(104mg, 0.5mmol) were dissolved in anhydrous tetrahydrofuran and DBU(76mg, 0.5mmol) was added. The mixture was stirred at room temperature for 2 hours and concentrated under the reduced pressure to remove tetrahydrofuran. The concentrate was purified by column chromatography(ethylacetate : hexane = 1 : 2) to obtain the titled compound.

yield : 59%

m.p. : 167-169℃

^{1}H NMR($CDCl_3$) δ : 2.21(3H,s), 2.43(6H,s), 3.06(4H,t), 3.68(4H,t), 4.09(3H,s), 6.89(1H,s), 7.06(1H,m), 7.14(3H,s), 8.26(1H,s)

Example 2

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-isopropenylphenyl)piperazine :

Phenyl N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate and 1-(2-isopropenylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield: 62 %

m.p. : 139-140℃

^{1}H NMR($CDCl_3$) δ : 2.20(3H,s), 2.21(6H,s), 3.10(4H,t), 3.64(4H,t), 3.84(3H,s), 5.07(1H,s), 5.13(1H,s), 6.64(1H,s), 6.98(1H,s), 7.04(3H,dd), 7.18(1H,d), 7.91(1H,s)

Example 3

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2,3,5,6-tetramethylphenyl)piperazine:

Phenyl N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate and 1-(2,3,5,6-tetramethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 71%

m.p. : 190-192℃

^{1}H NMR($CDCl_3$) δ : 2.21(15H,s), 2.42(3H,s), 3.17(4H,t), 3.61(4H,t), 4.08(3H,s), 6.84(1H,s), 6.89(1H,s), 8.26(1H,s)

Example 4

1-[(5-Ethyl-6-methyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methylthiophenyl)piperazine:

Phenyl N-(5-ethyl-6-methyl-2-methoxypyridin-3-yl)carbamate and 1-(2-methylthiophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 56%

m.p. : 160-161℃

^{1}H NMR($CDCl_3$) δ : 1.19(3H,t), 2.43(3H,s), 2.50(3H,s), 2.58(2H,q), 3.07(4H,t), 3.69(4H,t), 4.15(3H,s), 6.93(1H,s), 7.06(1H,m), 7.14(3H,m), 8.35(1H,s)

Mass(EI) m/z : Calcd for $C_{21}H_{28}N_4O_2$ 400.1932, found 400.1925

Example 5

1-[(5-Ethyl-6-methyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-isopropenylphenyl)piperazine:

Phenyl N-(5-ethyl-6-methyl-2-methoxypyridin-3-yl)carbamate and 1-(2-isopropenylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 51%

m.p. : 185-187℃

^{1}H NMR($CDCl_3$) δ : 1.18(3H,t), 2.21(3H,s), 2.42(3H,s), 2.56(2H,q), 3.08(4H,t), 3.62(4H,t), 4.03(3H,s), 5.08(1H,s), 5.13(1H,s), 6.90(1H,s), 7.02(3H,m), 7.18(1H,d), 8.25(1H,s)

Example 6

1-[(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2,3,5,6-tetramethylphenyl)piperazine:

Phenyl N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2,3,5,6-tetramethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 69%

m.p. : 176-177℃

^{1}H NMR($CDCl_3$) δ : 1.19(3H,t), 2.21(12H,s), 2.44(3H,s), 2.57(2H,q), 3.17(4H,t), 3.62(4H,t), 4.06(3H,s), 6.84(1H,s), 6.92(1H,s), 8.30(1H,s)

Example 7

1-[(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3-thiophenyl)piperazine:

Phenyl N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3-thiophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 63%

m.p. : 108-110℃

^{1}H NMR($CDCl_3$) δ : 1.17(3H,t), 2.37(3H,s), 2.49(2H,q), 3.28(4H,t), 3.60(4H,t), 3.98(3H,s), 6.87(4H,m), 6.98(1H,s), 8.18(1H,s)

Example 8

1-[(2-Methoxy-6-methyl-5-propylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(2-methoxy-6-methyl-5-propylpyridin-3-yl)carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 67%

m.p. : 82-84℃

^{1}H NMR($CDCl_3$) δ : 0.94(3H,t), 1.58(2H,m), 2.37(3H,s), 2.49(2H,q),

3.25(4H,t), 3.66(4H,t), 3.78(6H,s), 3.99(3H,s), 6.07(3H,m), 6.88(1H,s), 8.16(1H,s)

Mass(EI) m/z : Calcd for $C_{23}H_{32}N_4O_1$ 428.2423, found 428.2447

Example 9

1-[(2-Methoxy-6-methyl-5-propylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine

Phenyl N-(2-methoxy-6-methyl-5-propylpyridin-3-yl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 64%

m.p. : 145-146℃

^{1}H NMR($CDCl_3$) δ : 0.95(3H,t), 1.59(2H,m), 2.29(6H,s), 2.41(3H,s), 2.49(2H,q), 3.24(4H,t), 3.67(4H,t), 3.98(3H,s), 6.59(3H,m), 6.89(1H,s), 8.17(1H,s)

Mass(EI) m/z : Calcd for $C_{23}H_{32}N_4O_4$ 428.2423, found 428.2385

Example 10

1-[(2-Methoxy-6-methyl-5-propylpyridin-3-yl)aminocarbonyl]-4-(3,5-difluorophenyl)piperazine:

Phenyl N-(2-methoxy-6-methyl-5-propylpyridin-3-yl)carbamate and 1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 57%

m.p. : 121-123℃

^{1}H NMR($CDCl_3$) δ : 0.95(3H,t), 1.59(2H,m), 2.38(3H,s), 2.50(2H,q), 3.29(3H,t), 3.66(3H,t), 4.00(3H,s), 6.28(1H,m), 6.36(2H,d), 6.87(1H,s), 8.17(1H,s)

Example 11

1-[(2-Methoxy-6-methyl-5-propylpyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:

Phenyl N-(2-methoxy-6-methyl-5-propylpyridin-3-yl)carbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 71%

m.p. : 109-110℃

^{1}H NMR($CDCl_3$) δ : 0.95(3H,t), 1.59(2H,m), 2.37(3H,s), 2.49(2H,q), 3.12(4H,t), 3.70(4H,t), 3.89(3H,s), 3.97(3H,s), 6.91(4H,m), 6.95(1H,s), 8.19(1H,s)

Example 12

1-[(6-Ethyl-2-methoxy-5-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(6-ethyl-2-methoxy-5-methylpyridin-3-yl)carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 65%

m.p. : 115-116℃

^{1}H NMR($CDCl_3$) δ : 1.21(3H,t), 2.21(3H,s), 2.65(2H,q), 3.27(4H,t), 3.64(4H,t), 3.79(6H,s), 3.98(3H,s), 6.09(3H,m), 6.86(1H,s), 8.12(1H,s)

Mass(EI) m/z : Calcd for $C_{22}H_{30}N_4O_4$ 414.2267, found 414.2240

Example 13

1-[(6-Ethyl-2-methoxy-5-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(6-ethyl-2-methoxy-5-methylpyridin-3-yl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 61%

m.p. : 135-136℃

^{1}H NMR($CDCl_3$) δ : 1.22(3H,t), 2.21(3H,s), 2.29(6H,s), 2.65(2H,q), 3.24(4H,t), 3.66(4H,t), 3.98(3H,s), 6.59(3H,m), 6.87(1H,s), 8.12(1H,s)

Mass(EI) m/z : Calcd for $C_{22}H_{30}N_4O_2$ 382.2368, found 382.2376

Example 14

1-[(6-Ethyl-2-methoxy-5-methylpyridin-3-yl)aminocarbonyl]-4-(3-hydroxyphenyl)piperazine:

Phenyl N-(6-ethyl-2-methoxy-5-methylpyridin-3-yl)carbamate and 1-(3-hydroxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 56%

m.p. : 168-170℃

^{1}H NMR($CDCl_3$) δ : 1.21(3H,t), 2.20(2H,s), 2.63(2H,t), 3.28(4H,t), 3.68(4H,t), 3.98(3H,s), 6.41(1H,d), 6.55(1H,d), 6.84(1H,m), 6.87(1H,s), 7.13(1H,t), 8.10(1H,s)

Mass(EI) m/z : Calcd for $C_{20}H_{26}N_4O_3$ 370.2004, found 370.1992

Example 15

1-[(2-Methoxy-5-methyl-6-propylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(2-methoxy-5-methyl-6-propylpyridin-3-yl)carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 57%

m.p : 121-122℃

^{1}H NMR($CDCl_3$) δ : 0.96(3H,t), 1.67(2H,m), 2.21(3H,s), 2.58(2H,t), 3.26(4H,t), 3.68(4H,t), 3.79(6H,s), 3.97(3H,s), 6.14(3H,m), 6.89(1H,s), 8.11(1H,s)

Mass(EI) m/z : Calcd for $C_{23}H_{32}N_4O_4$ 428.2423, found 428.2423

Example 16

1-[(2-Methoxy-5-methyl-6-propylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(2-methoxy-5-methyl-6-propylpyridin-3-yl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 54%

m.p. : 138-139℃

^{1}H NMR($CDCl_3$) δ : 0.96(3H,t), 1.72(2H,m), 2.21(6H,s), 2.30(3H,s), 2.59(2H,t), 3.28(4H,t), 3.76(4H,t), 3.97(3H,s), 6.70(3H,m), 6.87(1H,s), 8.11(1H,s)

Mass(EI) m/z : Calcd for $C_{23}H_{32}N_4O_2$ 396.2525, found 396.2432

Example 17

1-[(2-Methoxy-5-methyl-6-propylpyridin-3-yl)aminocarbonyl]-4-(3-hydroxyphenyl)piperazine:

Phenyl N-(2-methoxy-5-methyl-6-propylpyridin-3-yl)carbamate and 1-(3-hydroxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 52%

m.p. : 153-155℃

^{1}H NMR($CDCl_3$) δ : 0.95(3H,t), 1.69(2H,m), 2.19(3H,s), 2.59(2H,t), 3.22(4H,t), 3.68(4H,t), 3.97(3H,s), 6.42(1H,d), 6.52(1H,d), 6.87(1H,s), 7.12(1H,t), 8.09(1H,s)

Mass(EI) m/z : Calcd for $C_{21}H_{28}N_4O_3$ 384.2161, found 384.2153

Example 18

1-[N-(2-Methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl) aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(2-methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl) carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 59%

m.p. : 143-144℃

^{1}H NMR($CDCl_3$) δ : 2.10(2H,m), 2.87(4H,m), 3.12(4H,t), 3.70(4H,t), 3.78(6H,s), 4.00(3H,s), 6.08(3H,m), 6.90(1H,s), 8.24(1H,s)

Example 19

1-[N-(2-Methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl) aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(2-methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl) carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 55%

m.p. : 183-185℃

^{1}H NMR($CDCl_3$) δ : 2.08(2H,m), 2.28(6H,s), 2.87(4H,m), 3.22(4H,t), 3.67(4H,t), 4.00(3H,s), 6.57(3H,m), 6.89(1H,s), 8.24(1H,s)

Example 20

1-[(2-Methoxy-5,6,7,8-tetrahydroquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(2-methoxy-5,6,7,8-tetrahydroquinoline-3-yl)carbamate and

1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 54%

m.p. : 161-163℃

^{1}H NMR($CDCl_3$) δ : 1.75(2H,m), 1.84(2H,m), 2.67(2H,t), 2.73(2H,t), 3.27(4H,t), 3.71(4H,t), 3.79(6H,s), 3.97(3H,s), 6.10(3H,m), 6.90(1H,s), 8.07(1H,s)

Example 21

1-[(2-Methoxy-5,6,7,8-tetrahydroquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethyphenyl)piperazine:

Phenyl N-(2-methoxy-5,6,7,8-tetrahydroquinolin-3-yl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 51%

m.p. : 143-144℃

^{1}H NMR($CDCl_3$) δ : 1.75(2H,m), 1.84(2H,m), 2.30(6H,s), 2.68(2H,t), 2.72(2H,t), 3.26(4H,t), 3.67(4H,t), 3.97(3H,s), 6.61(3H,m), 6.91(1H,s), 8.07(1H,s)

Example 22

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(5,6-dimethyl-2-methoxypyridin-3-yl)thiocarbamate(200mg, 0.7mmol) and 1-(3,5-dimethylphenyl)piperazine(154mg, 0.7mmol) were dissolved in anhydrous tetrahydrofuran and DBU(106mg) was added thereto. The mixture was stirred at room temperature for 2 hours and concentrated under the reduced pressure to remove the solvent. The concentrate was purified by column chromatography(ethylacetate : hexane = 1 : 2) to obtain the titled compound.

yield : 50%

m.p. : 192-193℃

^{1}H NMR($CDCl_3$) δ : 2.21(3H,s), 2.29(6H,s), 2.36(3H,s), 3.33(4H,t), 3.96(3H,s), 4.09(4H,t), 6.57(3H,m), 7.33(1H,s), 8.11(1H,s)

Mass(EI) m/z : Calcd for $C_{21}H_{28}N_4O_1S_1$ 384.1983, found 384.1992

Example 23

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminothiocarbonyl]-4-(3,5-difluorophenyl)piperazine:

Phenyl N-(5,6-dimethyl-2-methoxypyridin-3-yl)thiocarbamate and 1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.

yield : 47%

m.p. : 60-62℃

^{1}H NMR($CDCl_3$) δ : 2.21(3H,s), 2.36(3H,s), 3.39(4H,t), 3.96(3H,s), 4.10(3H,t), 6.29(3H,m), 7.33(1H,s), 8.14(1H,s)

Example 24

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminothiocarbonyl]-4-(3-hydroxyphenyl)piperazine:

Phenyl N-(5,6-dimethyl-2-methoxypyridin-3-yl)thiocarbamate and 1-(3-hydroxyphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.

yield : 43%

m.p. : 185-186℃

^{1}H NMR($CDCl_3$) δ : 2.14(3H,s), 2.36(3H,s), 3.25(4H,t), 3.89(3H,s), 4.09(4H,t), 6.30(1H,d), 6.36(2H,m), 7.03(1H,t), 7.48(1H,s), 8.56(1H,s)

Example 25

1-[(2-Methoxy-6-methyl-5-propylpyridin-3-yl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(2-methoxy-6-methyl-5-propylpyridin-3-yl)thiocarbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.

yield : 55%

m.p. : 143-144℃

^{1}H NMR($CDCl_3$) δ : 0.93(3H,t), 1.66(2H,m), 2.17(3H,s), 2.65(2H,t), 3.38(4H,t), 3.79(6H,s), 3.98(3H,s), 4.15(4H,t), 6.11(3H,m), 7.43(1H,s), 8.25(1H,s)

Example 26

1-[(2-Methoxy-5-methyl-6-propylpyridin-3-yl)aminothiocarbonyl]-4-(3,5

-dimethoxyphenyl)piperazine:

Phenyl N-(2-methoxy-5-methyl-6-propylpyridin-3-yl)thiocarbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.

yield : 52%

m.p. : 183-184℃

^{1}H NMR($CDCl_3$) δ : 0.98(3H,t), 1.72(2H,m), 2.17(3H,s), 2.62(2H,t), 3.39(4H,t), 3.79(6H,s), 3.96(3H,s), 4.19(4H,t), 6.15(3H,m), 7.42(1H,s), 8.08(1H,s)

Mass(EI) m/z : Calcd for $C_{23}H_{32}N_4O_3S_1$ 444.2195, found 444.2171

Example 27

1-[(2-Methoxy-5-methyl-6-propylpyridin-3-yl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(2-methoxy-5-methyl-6-propylpyridin-3-yl)thiocarbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.

yield : 49%

m.p. : 195-197℃

^{1}H NMR($CDCl_3$) δ : 0.98(3H,t), 1.73(2H,m), 2.18(6H,s), 2.34(3H,s), 2.62(2H,t), 3.47(4H,t), 3.96(3H,s), 4.01(4H,t), 6.59(3H,m), 7.02(1H,s), 7.99(1H,s)

Mass(EI) m/z : Calcd for $C_{23}H_{32}N_4O_1S_1$ 412.2296, found 412.2266

Example 28

1-[(2-Methoxy-5-methyl-6-propylpyridin-3-yl)aminothiocarbonyl]-4-(3-hydroxyphenyl)piperazine:

Phenyl N-(2-methoxy-5-methyl-6-propylpyridin-3-yl)thiocarbamate and 1-(3-hydroxyphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.

yield : 48%

m.p. : 160-162℃

^{1}H NMR($CDCl_3$) δ : 0.98(3H,t), 1.72(2H,m), 2.22(3H,s), 2.61(3H,t), 3.31(4H,t), 3.95(3H,s), 4.10(4H,t), 6.45(3H,m), 7.12(1H,t), 7.41(1H,s), 8.08(1H,s)

Mass(EI) m/z : Calcd for $C_{21}H_{28}N_4O_2S_1$ 400.1932, found 400.1969

Example 29

1-[N-(2-Methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(2-methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl) thiocarbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.

yield : 55%

m.p. : 169-170℃

^{1}H NMR($CDCl_3$) δ : 2.10(2H,m), 2.89(4H,m), 3.30(4H,t), 3.77(6H,s), 3.98(3H,s), 4.20(4H,t), 6.05(3H,m), 7.37(1H,s), 8.25(1H,s)

Example 30

1-[N-(2-Methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(2-methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl) thiocarbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.

yield : 53%

m.p. : 159-161℃

^{1}H NMR($CDCl_3$) δ : 2.09(2H,m), 2.28(6H,s), 2.87(4H,m), 3.67(4H,t), 4.00(3H,s), 4.21(4H,t), 6.57(3H,m), 6.93(1H,s), 8.24(1H,s)

Example 31

1-[(2-Methoxy-5,6,7,8-tetrahydroquinolin-3-yl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-[(2-methoxy-5,6,7,8-tetrahydroquinolin-3-yl)thiocarbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.

yield : 56%

m.p. : 160-161℃

^{1}H NMR($CDCl_3$) δ : 1.77(2H,m), 1.83(2H,m), 2.70(2H,t), 2.76(2H,t), 3.38(4H,t), 3.79(6H,s), 3.96(3H,s), 4.16(4H,t), 6.12(3H,m), 7.45(1H,s), 8.03(1H,s)

Example 32

1-[(2-Methoxy-5,6,7,8-tetrahydroquinolin-3-yl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(2-methoxy-5,6,7,8-tetrahydroquinolin-3-yl)thiocarbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.

yield : 54%

m.p. : 200-201℃

^{1}H NMR($CDCl_3$) δ : 1.77(2H,m), 1.84(2H,m), 2.34(6H,s), 2.71(3H,t), 2.75(3H,t), 3.47(4H,t), 3.97(3H,s), 4.42(4H,t), 6.35(3H,m), 6.91(1H,s), 7.91(1H,s)

Example 33

1-[(5,6-Dimethyl-2-methylaminopyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(5,6-dimethyl-2-methylaminopyridin-3-yl)carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 53%

m.p. : 150-151℃

^{1}H NMR($CDCl_3$) δ : 2.29(3H,s), 2.48(3H,s), 3.29(4H,t), 3.45(3H,s), 3.77(6H,s), 3.79(4H,t), 6.10(3H,m), 7.40(1H,s)

Example 34

1-[(5,6-Dimethyl-2-methylaminopyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(5,6-dimethyl-2-methylaminopyridin-3-yl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 52%

m.p. : 160-162℃

^{1}H NMR($CDCl_3$) δ : 2.30(9H,s), 2.48(3H,s), 3.31(4H,t), 3.46(3H,s), 3.78(4H,t), 6.60(3H,m), 7.41(1H,s)

Example 35

1-[(5-Ethyl-6-methyl-2-methylaminopyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(5-ethyl-6-methyl-2-methylaminopyridin-3-yl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 56%

m.p. : 143-145℃

^{1}H NMR($CDCl_3$) δ : 1.22(3H,t), 2.28(6H,s), 2.52(3H,s), 2.72(2H,q), 3.29(4H,t), 3.45(3H,s), 3.78(4H,t), 6.59(3H,m), 7.41(1H,s)

Example 36

1-[(2-Methylamino-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl) aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(2-methylamino-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl) carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 49%

m.p. : 148-150℃

^{1}H NMR($CDCl_3$) δ : 2.09(2H,m), 2.95(4H,m), 3.30(4H,t), 3.47(3H,s), 3.77(4H,t), 3.80(6H,s), 6.10(3H,m), 7.49(1H,s)

Example 37

1-[(2-Methylamino-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl) aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(2-methylamino-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl) carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 48%

m.p. : 185-187℃

^{1}H NMR($CDCl_3$) δ : 2.14(2H,m), 2.29(6H,s), 2.95(4H,m), 3.32(4H,t), 3.47(3H,s), 3.79(4H,t), 6.59(3H,m), 7.48(1H,s)

Example 38

1-{[5,6-Dimethyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl] aminocarbonyl}-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-[5,6-dimethyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl] carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 58%
m.p. : 74-75℃
^{1}H NMR($CDCl_3$) δ : 1.46(9H,s), 2.20(3H,s), 2.21(3H,s), 2.90(4H,t), 3.20(4H,t), 3.55(4H,t), 3.65(4H,t), 3.98(3H,s), 6.02(3H,m), 8.20(1H,s)

Example 39
1-{[5,6-Dimethyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl] aminocarbonyl}-4-(3,5-dimethylphenyl)piperazine:
Phenyl N-[5,6-dimethyl-2-(4'-butoxycarbonylpiperazinyl)pyridin-3-yl] carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield : 56%
m.p. : 155-156℃
^{1}H NMR($CDCl_3$) δ : 1.48(9H,s), 2.22(3H,s), 2.29(6H,s), 2.35(3H,s), 2.95(4H,t), 3.25(4H,t), 3.57(4H,t), 3.67(4H,t), 6.59(3H,m), 8.21(1H,s)

Example 40
1-{[5-Ethyl-6-methyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl] aminocarbonyl}-4-(3,5-dimethoxyphenyl)piperazine:
Phenyl N-[5-ethyl-6-methyl-2-(4'-t-butoxycarbonylpiperazinyl) pyridin-3-yl]carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield : 52%
m.p. : 119-120℃
^{1}H NMR($CDCl_3$) δ : 1.25(3H,t), 1.48(9H,s), 2.38(3H,s), 2.51(2H,q), 2.96(4H,t), 3.27(4H,t), 3.58(8H,m), 3.78(6H,s), 6.08(3H,m), 8.24(1H,s)

Example 41
1-{[5-Ethyl-6-methyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl] aminocarbonyl}-4-(3,5-dimethylphenyl)piperazine:
Phenyl N-[5-ethyl-6-methyl-2-(4'-t-butoxycarbonylpiperazinyl) pyridin-3-yl]carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield : 50%

m.p. : 126-128℃

^{1}H NMR($CDCl_3$) δ : 1.20(3H,t), 1.49(9H,s), 2.29(6H,s), 2.39(3H,s), 2.52(2H,q), 2.98(4H,t), 3.23(4H,t), 3.59(8H,m), 6.59(3H,m), 7.58(1H,s), 8.26(1H,s)

Example 42

1-[(5,6-Dimethyl-2-piperazinylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-{[5,6-Dimethyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl] aminocarbonyl}-4-(3,5-dimethoxyphenyl)piperazine(0.218g, 0.4mmol) was dissolved in dichloromethane : nitromethane = 2 : 1(10ml) and anisole(0.26g, 2.4mmol) and aluminum chloride(0.3g, 2.4mmol) were added slowly thereto. The mixture was stirred at room temperature for 20min. Distilled water(50ml) was added into the mixture and the mixture was made basic with saturated $NaHCO_3$ and extracted with dichloromethane and then concentrated under the reduced pressure to remove the solvent. The concentrate was purified by column chromatography(methanol : dichloromethane = 8:1) to obtain the titled compound.

yield : 89%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 2.21(3H,s), 2.35(3H,s), 3.02(4H,t), 3.34(4H,t), 3.59(4H,t), 3.62(4H,t), 3.78(6H,s), 6.08(3H,m), 8.18(1H,s)

Example 43

1-[(5,6-Dimethyl-2-piperazinylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-{[5,6-Dimethyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl] aminocarbonyl}-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 42 to obtain the titled compound.

yield : 85%

m.p. : 103-105℃

^{1}H NMR($CDCl_3$) δ : 2.16(3H,s), 2.24(6H,s), 2.40(3H,s), 3.30(4H,t), 3.44(4H,t), 3.50(4H,t), 3.81(4H,t), 6.95(3H,m), 7.72(1H,s)

Example 44

1-[(5-Ethyl-6-methyl-2-piperazinylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-{[5-Ethyl-6-methyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl]aminocarbonyl}-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 42 to obtain the titled compound.

yield : 88%

m.p. : 68-70℃

^{1}H NMR($CDCl_3$) δ : 1.20(3H,t), 2.40(3H,s), 2.52(2H,q), 2.75(4H,t), 3.32(4H,t), 3.70(8H,m), 3.78(6H,s), 6.09(3H,m), 7.68(1H,s), 8.23(1H,s)

Example 45

1-[(5-Ethyl-6-methyl-2-piperazinylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-{[5-Ethyl-6-methyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl]aminocarbonyl}-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 42 to obtain the titled compound.

yield : 85%

m.p. : 100-102℃

^{1}H NMR($CDCl_3$) δ : 1.20(3H,t), 2.28(6H,s), 2.39(3H,s), 2.65(2H,q), 2.76(4H,t), 3.00(4H,t), 3.23(4H,t), 3.70(4H,t), 6.58(3H,m), 7.66(1H,s), 8.24(1H,s)

Example 46

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)carbamate(200mg, 0.67mmol) and 1-(3,5-dimethoxyphenyl)piperazine(150mg, 0.67mmol) were dissolved in anhydrous tetrahydrofuran(15ml) and DBU(100mg, 0.67mmol) was added. The mixture was stirred at room temperature for 2 hrs and concentrated under the reduced pressure to remove tetrahydrofuran. The concentrate was purified by column chromatography(ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 83%

m.p. : 149-151℃

^{1}H NMR($CDCl_3$) δ : 2.57(3H,s), 2.65(3H,s), 3.28(4H,t,J=4.65Hz), 3.70(4H,t,

J=4.65Hz), 3.79(6H,s), 4.06(3H,s), 6.09(1H,s), 6.14(2H,d),6.94(1H,s), 8.87(1H,s)

Example 47

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 46 to obtain the titled compound.

yield : 82%

m.p. : 66-69°C

^{1}H NMR($CDCl_3$) δ : 2.31(6H,s), 2.57(3H,s), 2.65(3H,s), 3.08(4H,t), 3.30(4H,t), 4.10(3H,s), 6.71(2H,d), 6.94(1H,s), 8.89(1H,s)

Example 48

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-difluorophenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 46 to obtain the titled compound.

yield : 77%

m.p. : 180-181°C

^{1}H NMR($CDCl_3$) δ : 2.57(3H,s), 2.65(3H,s), 3.33(4H,t,J=5.0Hz), 3.74(4H,t, J=5.0Hz), 4.07(3H,s), 6.37(1H,s), 6.46(2H,d), 6.93(1H,s), 8.85(1H,s)

Example 49

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dichlorophenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 46 to obtain the titled compound.

yield : 81%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 2.57(3H,s), 2.65(3H,s), 3.34(4H,t), 3.78(4H,t), 4.04(3H,s), 6.93(3H,m), 8.80(1H,s)

Example 50

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2,3-dimethylphenyl)piperazine:

Pheny N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2,3-dimethylphenyl)piperazine were reacted by the same way with the example 46 to obtain the titled compound.

yield : 81%

m.p. : 173-174℃

^{1}H NMR($CDCl_3$) δ : 2.29(6H,s), 2.58(3H,s), 2.65(3H,s), 2.98(4H,t), 3.70(4H,t), 4.06(3H,s), 6.91(1H,d), 6.97(1H,s), 7.10(1H,t), 8.89(1H,s)

Example 51

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 46 to obtain the titled compound.

yield : 79%

m.p. : 153-154℃

^{1}H NMR($CDCl_3$) δ : 2.58(3H,s), 2.65(3H,s), 3.15(4H,t), 3.73(4H,t), 3.90(3H,s), 4.06(3H,s), 6.91(1H,d), 6.96(1H,d), 6.97(1H,s), 7.10(1H,t), 8.89(1H,s)

Example 52

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3-hydroxyphenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3-hydroxyphenyl)piperazine were reacted by the same way with the example 46 to obtain the titled compound.

yield : 76%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 2.60(3H,s), 2.72(3H,s), 3.34(4H,t), 3.79(4H,t), 3.98(3H,s), 6.45(3H,m), 6.98(1H,m), 8.97(1H,s)

Example 53

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminothiocarbonyl]-4-(3,5

-dimethoxyphenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)thiocarbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.

yield : 77%

m.p. : 167-169℃

^{1}H NMR($CDCl_3$) δ : 2.58(3H,s), 2.68(3H,s), 3.47(4H,t), 3.81(6H,s), 4.05(3H,s), 4.36(4H,t), 6.42(3H,m), 7.49(1H,s), 9.05(1H,s)

Example 54

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)thiocarbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.

yield : 75%

m.p. : 176-177℃

^{1}H NMR($CDCl_3$) δ : 2.34(6H,s), 2.58(3H,s), 2.68(3H,s), 3.48(4H,t), 4.06(3H,s), 4.43(4H,t), 7.05(3H,m), 7.52(1H,s), 9.04(1H,s)

Example 55

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminothiocarbonyl]-4-(3-hydroxyphenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)thiocarbamate and 1-(3-hydroxyphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.

yield : 71%

m.p. : 114-115℃

^{1}H NMR($CDCl_3$) δ : 2.56(3H,s), 2.75(3H,s), 3.68(4H,t), 4.05(3H,s), 4.45(4H,t), 7.30(4H,m), 9.03(1H,s)

Mass(EI) m/z : Calcd for $C_{23}H_{30}N_4O_4S_1$ 458.1987, found 458.2527

Example 56

1-{[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl}-4-(3,5-dimethoxyphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-

dimethoxyphenyl)piperazine(100mg, 0.23mmol) was dissolved in anhydrous ethanol(15ml) and $NaBH_4$(8.66mg) was added. The reaction solution was stirred at room temperature for 2 hours. The mixture was concentrated under the reduced pressure to remove ethanol and purified by column chromatography (ethylacetate : hexane = 2:1) to obtain the titled compound.

yield : 97%

m.p. : 124-126℃

^1H NMR($CDCl_3$) δ : 1.48(3H,d), 2.42(3H,s), 3.27(4H,t), 3.69(4H,t), 3.79(6H,s), 3.99(3H,s), 5.03(1H,q), 6.09(1H,s), 6.15(2H,d), 6.90(1H,s), 8.46(1H,s)

Mass(EI) m/z : Calcd for $C_{22}H_{30}N_4O_5$ 430.2216, found 430.2265

Example 57

1-([5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl)-4-(3,5-dimethylphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 56 to obtain the titled compound.

yield : 95%

m.p. : 153-154℃

^1H NMR($CDCl_3$) δ : 1.48(3H,d), 2.30(6H,s), 2.42(3H,s), 3.26(4H,t), 3.68(4H,t), 3.99(3H,s), 5.05(1H,q), 6.71(2H,d), 6.96(1H,s), 8.46(1H,s)

Mass(EI) m/z : Calcd for $C_{22}H_{30}N_4O_3$ 398.2317, found 398.2343

Example 58

1-([5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl)-4-(2,3-dimethylphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl]-4-(2,3-dimethylphenyl)piperazine was reacted by the same way with the example 56 to obtain the titled compound.

yield : 96%

m.p. : 100-102℃

^1H NMR($CDCl_3$) δ : 1.47(3H,d), 1.59(3H,s), 2.25(3H,s), 2.28(3H,s), 2.43(3H,s), 2.93(4H,t), 3.66(4H,t), 3.99(3H,s), 5.05(1H,q), 6.93(3H,m), 7.11(1H,m), 8.48(1H,s)

Example 59

1-{[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl}-4-(3,5-difluorophenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-difluorophenyl)piperazine was reacted by the same way with the example 56 to obtain the titled compound.

yield : 97%

m.p. : 184-186℃

^{1}H NMR($CDCl_3$) δ : 1.48(3H,d), 2.50(3H,s), 3.30(4H,t), 3.70(4H,t), 4.11(3H,s), 5.06(1H,q), 6.33(1H,s), 6.42(2H,d), 6.92(1H,s), 8.54(1H,s)

Example 60

1-{[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl}-4-(3,5-dichlorophenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dichlorophenyl)piperazine was reacted by the same way with the example 56 to obtain the titled compound.

yield : 95%

m.p. : 197-200℃

^{1}H NMR($CDCl_3$) δ : 1.46(3H,d), 2.41(3H,s), 3.28(4H,t), 3.66(4H,t), 3.96(3H,s), 5.20(1H,q), 7.02(3H,m), 8.42(1H,s)

Example 61

1-{[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl}-4-(2-methoxyphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine was reacted by the same way with the example 56 to obtain the titled compound.

yield : 97%

m.p. : 88-90℃

^{1}H NMR($CDCl_3$) δ : 1.47(3H,d), 2.42(3H,s), 3.11(4H,t), 3.70(4H,t), 3.89(3H,s), 3.99(3H,s), 5.03(1H,q), 6.89(3H,m), 6.94(1H,s), 7.05(1H,m), 8.48(1H,s)

Example 62

1-{[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl}-4-(3-hydroxyphenyl)piperazine:

1-[5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3-hydroxyphenyl)piperazine was reacted by the same way with the example 56 to obtain the titled compound.

yield : 87%

m.p. : 194-196℃

^{1}H NMR($CDCl_3$) δ : 1.47(3H,d), 2.41(3H,s), 3.27(4H,t), 3.79(4H,t), 3.98(3H,s), 5.04(1H,q), 6.57(3H,m), 6.90(1H,s), 7.13(1H,t), 8.41(1H,s)

Example 63

1-{[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminothiocarbonyl}-4-(3,5-dimethoxyphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 56 to obtain the titled compound.

yield : 89%

m.p. : 189-190℃

^{1}H NMR($CDCl_3$) δ : 1.47(3H,d), 2.43(3H,s), 3.35(4H,t), 3.78(6H,s), 3.97(3H,s), 4.09(4H,t), 5.05(1H,q), 6.07(3H,m), 7.35(1H,s), 8.42(1H,s)

Example 64

1-{[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminothiocarbonyl}-4-(3,5-dimethylphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 56 to obtain the titled compound.

yield : 88%

m.p. : 170-172℃

^{1}H NMR($CDCl_3$) δ : 1.46(3H,d), 2.29(6H,s), 2.43(3H,s), 3.43(4H,t), 3.97(3H,s), 4.10(4H,t), 5.06(1H,q), 6.60(3H,m), 7.37(1H,s), 8.40(1H,s)

Example 65

1-{[5-(1-Hydroxy-1-methylethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl}-4-(3,5-dimethoxyphenyl)piperazine:

1-((5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-

dimethoxyphenyl)piperazine(214mg, 0.50mmol) was dissolved in tetrahydrofuran(10ml) and CH_3MgBr(0.50ml, 1.50mmol) was added slowly. The mixture solution was refluxed for 15 hrs and concentrated under the reduced pressure to remove the solvent and extracted with ethylacetate, dried and filtered. The resultant was purified by column chromatography(ethylacetate : hexane = 1: 2) to obtain the titled compound.

yield : 84%

m.p. : 146-148℃

^1H NMR($CDCl_3$) δ : 1.64(6H,s), 2.64(3H,s), 3.25(4H,t), 3.67(4H,t), 3.78(6H,s), 3.99(3H,s), 6.07(3H,m), 6.86(1H,s), 8.47(1H,s)

Example 66

1-{[5-(1-Hydroxy-1-methylethyl)-2-methoxy-6-methylpyridin-3-yl] aminocarbonyl}-4-(3,5-dimethylphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 65 to obtain the titled compound.

yield : 81%

m.p. : oil phase

^1H NMR($CDCl_3$) δ : 1.64(6H,s), 2.29(6H,s), 2.65(3H,s), 3.24(4H,t), 3.67(4H,t), 3.99(3H,s), 6.59(3H,m), 7.05(1H,s), 8.48(1H,s)

Example 67

1-{[5-(1-Hydroxy-1-methylpropyl)-2-methoxy-6-methylpyridin-3-yl] aminocarbonyl}-4-(3,5-dimethoxyphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(214mg, 0.50mmol) was dissolved in tetrahydrofuran(10ml) and C_2H_5MgBr(0.50mg, 1.50mmol) was added slowly. The mixture solution was refluxed for 15 hours and concentrated under the reduced pressure to remove the solvent and extracted with ethylacetate, dried and filtered. The resultant was purified by column chromatography(ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 76%

m.p. : 127-129℃

^{1}H NMR($CDCl_3$) δ : 0.83(3H,t), 1.63(3H,s), 1.94(2H,m), 2.61(3H,s), 3.26(4H,t), 3.68(4H,t), 3.79(6H,s), 3.99(3H,s), 6.08(3H,m), 6.86(1H,s), 8.44(1H,s)

Example 68

1-([5-(1-Hydroxy-1-methylpropyl)-2-methoxy-6-methylpyridin-3-yl] aminocarbonyl)-4-(3,5-dimethylphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 67 to obtain the titled compound.

yield : 74%

m.p. : 164-165℃

^{1}H NMR($CDCl_3$) δ : 0.83(3H,t), 1.60(3H,s), 1.95(2H,m), 2.29(6H,s), 2.61(3H,s), 3.23(4H,t), 3.67(4H,t), 3.99(3H,s), 6.59(3H,m), 6.87(1H,s), 8.45(1H,s)

Example 69

1-[5-(([4-(3,5-Dimethoxyphenyl)piperazino]carbonyl)amino)-6-methoxy-2-methylpyridin-3-yl]ethyl ethanthioate:

Triphenylphosphine(262mg, 1.0mmol) was dissolved in tetrahydrofuran(15ml) and diethyl azodicarboxylate(157$\mu\ell$, 1.0mmol) was added and then the mixture was stirred at 0℃ for 30min.

1-([5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl)-4-(3,5-dimethoxyphenyl)piperazine(213mg, 0.5mmol) and thioacetic acid(72$\mu\ell$, 1.0mmol) were dissolved in tetrahydrofuran and was added into the above solution. The mixture solution was stirred at 0℃ for 1hour and at room temperature for 1hour and then was concentrated under the reduced pressure to remove the solvent. The concentrate was purified by column chromatography(ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 62%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 1.55(3H,d), 2.20(3H,s), 2.39(3H,s), 3.15(4H,t), 3.57(4H,t), 3.69(6H,s), 3.90(3H,s), 4.74(1H,q), 6.01(3H,m), 6.89(1H,s), 8.33(1H,s)

Example 70

1-[5-(([4-(3,5-Dimethylphenyl)piperazino]carbonyl}amino)-6-methoxy-2-methylpyridin-3-yl]ethyl ethanthioate:

1-{[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl} -4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 69 to obtain the titled compound.

yield : 60%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 1.60(3H,d), 2.26(6H,s), 2.52(3H,s), 3.20(4H,t), 3.64(4H,t), 3.96(3H,s), 4.80(1H,q), 6.56(3H,m), 6.91(1H,s), 8.38(1H,s)

Example 71

1-{[2-Methoxy-6-methyl-5-(1-sulfanylmethyl)]aminocarbonyl}-4-(3,5-dimethoxyphenyl)piperazine:

1-[5-(([4-(3,5-Dimethoxyphenyl)piperazino]carbonyl}amino)-6-methoxy-2 -methylpyridin-3-yl]ethyl ethanthioate(180mg, 0.37mmol) was dissolved in tetrahydrofuran(15ml) and $LiAlH_4$(15mg, 0.4mmol) was added and then the mixture was stirred at 0℃ for 20min. 2N-HCl was added the above solution. The mixture was concentrated under the reduced pressure to remove the solvent and extracted with dichloromethane, dried and filtered. The resultant was concentrated under the reduced pressure and purified by column chromatography(ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 88%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 1.42(3H,d), 2.39(3H,s), 3.25(4H,t), 3.66(4H,t), 3.76(6H,s), 3.96(3H,s), 5.02(1H,q), 6.17(3H,m), 6.87(1H,s), 8.41(1H,s)

Example 72

1-{[2-Methoxy-6-methyl-5-(1-sulfanylmethyl)]aminocarbonyl}-4-(3,5-dimethylphenyl)piperazine:

1-[5-(([4-(3,5-Dimethylphenyl)piperazino]carbonyl}amino)-6-methoxy-2-methylpyridin-3-yl]ethyl ethanthioate was reacted by the same way with the example 71 to obtain the titled compound.

yield : 87%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 1.43(3H,d), 2.28(6H,s), 2.40(3H,s), 3.25(4H,t), 3.72(4H,t), 5.03(1H,q), 6.64(3H,m), 6.88(1H,s), 8.42(1H,s)

Exmaple 73

1-[(2-Methoxy-6-methyl-5-vinylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-{[5-(1-Hydroxyethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl}-4-(3,5-dimethoxyphenyl)piperazine was dissolved in chloroform(15ml) and pyridinum p-toluensulfonate(60mg, 0.23mmol) was added and then the mixture solution was refluxed 16hours. The above solution was concentrated under the reduced pressure to remove chloroform and purified by column chromatography to obtain the titled compound.

yield : 93%

m.p. : 140-141°C

^{1}H NMR($CDCl_3$) δ : 2.43(3H,s), 3.27(4H,t), 3.69(4H,t), 3.79(6H,s), 4.00(3H,s), 5.25(1H,d), 5.65(1H,d), 6.08(1H,s), 6.13(2H,d), 6.82(1H,d), 6.91(1H,s), 8.53(1H,s)

Mass(EI) m/z : Calcd for $C_{22}H_{28}N_4O_4$ 412.2110, found 412.2119

Example 74

1-[(2-Methoxy-6-methyl-5-vinylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-{[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl}-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 73 to obtain the titled compound.

yield : 94%

m.p. : 131-132°C

^{1}H NMR($CDCl_3$) δ : 1.57(3H,s), 2.31(6H,s), 2.43(1H,s), 3.25(4H,t), 3.68(4H,t), 4.00(3H,s), 5.25(1H,d), 5.65(1H,d) 6.60(3H,m), 6.82(1H,dd), 6.92(1H,s), 8.53(1H,s)

Mass(EI) m/z : Calcd for $C_{22}H_{28}N_4O_2$ 380.2212, found 380.2236

Example 75

1-[(2-Methoxy-6-methyl-5-vinylpyridin-3-yl)aminocarbonyl]-4-(3,5-difluorophenyl)piperazine:

1-{[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl}

-4-(3,5-difluorophenyl)piperazine was reacted by the same way with the example 73 to obtain the titled compound.

yield : 93%

m.p. : 160-161℃

^{1}H NMR($CDCl_3$) δ : 2.44(3H,s), 3.30(4H,t,J=5.5Hz), 3.68(4H,t,J=5.5Hz), 4.01(3H,s), 5.26(1H,d), 5.65(1H,d), 6.30(1H,s), 6.39(2H,d), 6.81(1H,dd), 8.53(1H,s)

Mass(EI) m/z : Calcd for $C_{22}H_{28}N_4O_4$ 412.2110, found 412.2102

Example 76

1-[(5-Isopropenyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

-{[5-(1-Hydroxy-1-methylethyl)-2-methoxy-6-methylpyridin-3-yl) aminocarbonyl]}-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 73 to obtain the titled compound.

yield : 96%

m.p. : 83-85℃

^{1}H NMR($CDCl_3$) δ : 2.01(3H,s), 2.38(3H,s), 3.25(4H,t), 3.66(4H,t), 3.78(6H,s), 3.99(3H,s), 4.86(1H,s), 5.30(1H,s), 6.11(3H,m), 6.90(1H,s), 8.18(1H,s)

Example 77

1-[(5-Isopropenyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-{[5-(1-Hydroxy-1-methylethyl)-2-methoxy-6-methylpyridin-3-yl]amin ocarbonyl}-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with example 73 to obtain the titled compound.

yield : 93%

m.p. : 140-142℃

^{1}H NMR($CDCl_3$) δ : 2.01(3H,s), 2.29(6H,s), 2.28(3H,s), 3.23(4H,t), 3.66(4H,t), 3.99(3H,s), 4.86(1H,s), 5.18(1H,s), 6.59(3H,m), 6.91(1H,s), 8.18(1H,s)

Example 78

Ethyl 2-(1-[5-(([4-(3,5-dimethoxyphenyl)piperazino]carbonyl}amino)-6-methoxy-2-methylpyridin-3-yl]ethoxy)acetate:

1-{[5-(1-Hydroxy)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl}-4-(3,5-dimethoxyphenyl)piperazine(0.5mmol) was dissolved in dimethylformamide(15ml) and NaH(18.5mg, 0.5mmol) was added and then the mixture solution was stirred at room temperature for 15min. Ethylbromoacetate(83.5mg, 0.5mmol) was added into the above mixture and stirred at room temperature for 3hours. The mixture was concentrated under the reduced pressure to remove the solvent and purified by column chromatography(ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 89%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 1.25(3H,t), 1.34(3H,d), 2.42(3H,s), 3.00(4H,t), 3.29(4H,t), 3.74(6H,s), 3.97(3H,s), 4.16(4H,s), 4.53(1H,q), 6.03(3H,m), 7.58(1H,s)

Example 79

4-{1-[5-({[4-(3,5-Dimethoxyphenyl)piperazino]carbonyl}amino)-6-methoxy-2-methylpyridin-3-yl]ethoxy}-4-oxobutanoic acid:

1-{[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl}-4-(3,5-dimethoxyphenyl)piperazine(107mg, 0.25mmol) and dimethylaminopyridine(3mg, 0.025mmol) were dissolved in pyridine and anhydrous succinic acid(50mg, 0.5mmol) was added. The mixture was stirred at room temperature for 5hrs. Distilled water was added into the above mixture. The above solution was extracted with CH_2Cl_2 and the organic phase washed with 1N-HCl and then concentrated under the reduced pressure to remove the solvent. The concentrate was purified by column chromatography(dichloromethane : methanol = 20:1) to obtain the titled compound.

yield : 78%

m.p. : 158-160℃

^{1}H NMR($CDCl_3$) δ : 1.42(3H,d), 2.43(3H,s), 2.61(4H,m), 3.24(4H,t), 3.66(4H,t), 3.76(6H,s), 3.95(3H,s), 5.94(1H,q), 6.04(3H,m), 6.89(1H,s), 8.13(1H,s)

Example 80

4-{1-[5-({[4-(3,5-Dimethylphenyl)piperazino]carbonyl}amino)-6-methoxy-

2-methylpyridin-3-yl]ethoxy)-4-oxobutanoic acid:
1-{[5-(1-hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl}-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 79 to obtain the titled compound.
yield : 76%
m.p. : 138-140℃
^{1}H NMR($CDCl_3$) δ : 1.43(3H,d), 2.27(6H,s), 2.55(3H,s), 2.65(4H,m), 3.24(4H,t), 3.69(4H,t), 3.95(3H,s), 5.95(1H,q), 6.60(3H,m), 6.88(1H,s), 8.11(1H,s)

Example 81
1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl) piperazine:

a) Phenyl N-(2-methoxyquinolin-3-yl)carbamate:
3-Amino-2-methoxyquinoline(4g, 23mmol) and phenyl chloroformate(4.04g, 25mmol) were dissolved in dichloromethane and stirred at room temperature for 2 hours. The above mixture was concentrated under the reduced pressure to remove dichloromethane and purified by column chromatography(hexane : ether =8:1) to obtain the titled compound.
yield : 75%
m.p. : oil phase
^{1}H NMR ($CDCl_3$): δ 4.01(3H,s), 7.30(5H,s), 7.41(1H,t), 7.70(1H,d), 7.71(1H,d), 8.71(1H,s)

b) 1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl) piperazine:
Phenyl N-(2-methoxyquinolin-3-yl)carbamate(148mg, 0.5mmol) and 1-(3,5-dimethoxyphenyl)piperazine(112mg, 0.5mmol) were dissolved in anhydrous tetrahydrofuran and DBU(117mg, 0.75mmol) was added. The solution was stirred at room temperature for 2 hours. The mixture was concentrated under the reduced pressure to remove tetrahydrofuran and purified by column chromatography(hexane : ether = 5:1) to obtain the titled compound.
yield : 81%

m.p. : 200-201℃

^{1}H NMR ($CDCl_3$): δ 3.31(4H,t,J=5.0Hz), 3.74(4H,t), 3.79(6H,s), 4.17(3H,s), 6.09(1H,s), 6.17(2H,s), 7.35(1H,t), 7.49(1H,t), 7.71(1H,d), 7.78(1H,d), 8.78(1H,s)

Mass(EI) m/z : Calcd for $C_{23}H_{26}N_4O_4$ 422.1954, found 422.1952

Example 82

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl) piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 79%

m.p. : 143-145℃

^{1}H NMR ($CDCl_3$): δ 2.30(6H,s), 3.29(4H,t), 3.80(4H,t), 4.18(3H,s), 6.62(3H,m), 7.36(1H,t), 7.49(1H,t), 7.71(1H,d), 7.78(1H,d), 8.79(1H,s)

Mass(EI) m/z : Calcd for $C_{23}H_{26}N_4O_2$ 390.2055, found 390.2066

Example 83

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(2,3-dimethylphenyl) piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and 1-(2,3-dimethylphenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 83%

m.p. : 174-175℃

^{1}H NMR ($CDCl_3$): δ 2.20(3H,s), 2.39(3H,s), 3.28(4H,t), 3.69(4H,t), 3.93(3H,s), 5.98(1H,s), 6.30(1H,t), 6.37(1H,s), 6.39(1H,s), 6.63(1H,s)

Example 84

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-difluorophenyl) piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and 1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 78%

m.p. : 158-159℃

^{1}H NMR ($CDCl_3$): δ 3.32(4H,t,J=5.0Hz), 3.72(4H,t,J=5.0Hz), 4.19(3H,s), 6.29(1H,s), 6.39(2H,d), 7.36(1H,t), 7.50(1H,t), 7.71(1H,d), 7.81(1H,d), 8.78(1H,s)

Example 85

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dichlorophenyl) piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and 1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 56%

m.p. : 156-158℃

^{1}H NMR ($CDCl_3$): δ 3.33(4H,t), 3.73(4H,t), 4.21(3H,s) 6.79(1H,s), 6.83(1H,d), 6.93(1H,t), 7.26(1H,t), 7.38(1H,t), 7.52(1H,t), 7.71(1H,d), 7.83(1H,d)

Mass(EI) m/z : Calcd for $C_{21}H_{20}N_4O_2Cl_1$ 430.0963, found 430.0977

Example 86

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(2-fluorophenyl)piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and 1-(2-fluorophenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 81%

m.p. : 156-158℃

^{1}H NMR ($CDCl_3$): δ 3.18(4H,t), 3.74(4H,t), 4.18(3H,s), 6.99(2H,q), 7.07(2H,m), 7.35(2H,m), 7.50(1H,t), 7.70(1H,d), 7.77(1H,d)

Example 87

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(2-chlorophenyl)piperazine:

Phenyl N-(2-methoxyquinoline-3-yl)carbamate and 1-(2-chlorophenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 78%

m.p. : 79-80℃

^{1}H NMR ($CDCl_3$): δ 3.32(4H,t), 3.74(4H,t), 4.20(3H,s), 6.82(2H,q),

6.94(2H,m), 7.34(2H,m), 7.48(1H,d), 7.70(1H,d), 7.78(1H,d)

Example 88

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3-chlorophenyl)piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and 1-(3-chlorophenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 73%

m.p. : 97-98℃

^{1}H NMR ($CDCl_3$): δ 3.31(4H,t), 3.73(4H,t), 4.18(3H,s), 6.82(1H,d), 6.87(1H,d), 6.92(1H,s), 7.21(1H,t), 7.32(1H,s), 7.37(1H,t), 7.51(1H,t), 7.70(1H,d), 7.78(1H,d), 8.80(1H,s)

Example 89

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3-hydroxyphenyl) piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and 1-(3-hydroxyphenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 75%

m.p. : 190-191℃

^{1}H NMR ($CDCl_3$): δ 3.33(4H,t), 3.80(4H,t), 4.19(3H,s), 6.47(1H,s), 6.62(2H,s), 7.16(1H,t), 7.32(1H,s), 7.37(1H,t), 7.51(1H,t), 7.72(1H,d), 7.78(1H,d), 8.78(1H,s)

Example 90

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl) piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 88%

m.p. : 159-161℃

^{1}H NMR ($CDCl_3$): δ 3.28(4H,t), 3.71(4H,t), 3.81(3H,s), 4.18(3H,s), 6.52(2H,s), 6.62(1H,s), 7.23(1H,t), 7.31-7.53(3H,m), 7.72(2H,m), 8.81(1H,s)

Example 91

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(2-methylthiophenyl) piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and 1-(2-methylthiophenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 78%

m.p. : 147-149℃

^{1}H NMR ($CDCl_3$): δ 2.44(3H,s), 3.07(4H,t), 3.75(4H,t), 4.18(3H,s), 7.13(3H,m), 7.18(1H,d), 7.39(2H,m), 7.70(3H,m), 8.81(1H,s)

Example 92

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3-isopropoxyphenyl) piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and 1-(3-isopropoxyphenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 93%

m.p. : 111-113℃

^{1}H NMR ($CDCl_3$): δ 1.34(6H,d), 3.30(4H,t), 3.74(4H,t), 4.18(3H,s), 4.55(1H,m), 6.49(2H,s), 7.05(1H,s), 7.20(1H,t), 7.32(1H,s), 7.37(1H,t), 7.50(1H,t), 7.70(1H,d), 7.77(1H,d), 8.80(1H,s)

Example 93

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3-cyclopropylmethoxy phenyl)piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and 1-(3-cyclopropylmethoxyphenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 90%

m.p. : 146-147℃

^{1}H NMR ($CDCl_3$): δ 0.36(2H,t), 0.65(2H,m), 1.28(1H,m), 3.31(4H,t), 3.75(4H,t), 3.80(2H,d), 4.18(3H,s), 6.50(1H,s), 6.60(2H,s), 7.19(1H,t), 7.32(1H,s), 7.37(1H,t), 7.50(1H,t), 7.70(1H,d), 7.77(1H,d), 8.79(1H,s)

Example 94

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(2-methoxy-5-methyl phenyl)piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and 1-(2-methoxy-5-methylphenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 76%

m.p. : 115-116℃

^{1}H NMR ($CDCl_3$): δ 2.30(3H,s), 3.14(4H,t), 3.75(4H,t), 3.87(3H,s), 4.18(3H,s), 6.79(2H,m), 6.84(1H,d), 7.35(2H,m), 7.50(1H,t), 7.72(1H,d), 7.77(1H,d), 8.82(1H,s)

Example 95

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(2-methoxy-5-phenyl phenyl)piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and 1-(2-methoxy-5-phenylphenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 77%

m.p. : 122-123℃

^{1}H NMR ($CDCl_3$): δ 3.38(4H,t) 3.86(4H,t), 3.97(3H,s), 4.18(3H,s), 7.05(2H,m), 7.34-7.45(6H,m), 7.50(1H,t), 7.56(2H,d), 7.71(2H,d), 7.78(2H,d), 8.88(1H,s)

Example 96

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(5-methoxy-2-methyl phenyl)piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and 1-(5-methoxy-2-methylphenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 82%

m.p. : 128-130℃

^{1}H NMR ($CDCl_3$): δ 2.30(3H,s), 3.37(4H,t), 3.84(4H,t), 3.78(3H,s), 3.97(3H,s), 7.05(2H,m), 7.13(1H,d), 7.38(3H,m), 7.62(1H,d), 7.80(1H,s), 8.88(1H,s)

Example 97

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(1-naphthyl)piperazine: Phenyl N-(2-methoxyquinolin-3-yl)carbamate and 1-(1-naphthyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 68%

m.p. : 158-160℃

^{1}H NMR ($CDCl_3$): δ 3.22(4H,t), 3.86(4H,t), 4.20(3H,s), 7.13(1H,d), 7.38(2H,m), 7.43(1H,t), 7.53(3H,m), 7.62(1H,d), 7.72(1H,d), 7.80(1H,d), 7.86(1H,d), 8.24(1H,d), 8.84(1H,s)

Example 98

1-[N-(2-Methoxyquinolin-3-yl)-N-methylaminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl) piperazine(106mg, 0.25mmol) was dissolved in dimethylformamide(15ml) and sodium hydride(6.0mg, 0.25mmol) was added and the solution was stirred at room temperature for 15 min. Iodomethane(35mg, 0.25mmol) was added to the above solution. The mixture was stirred at room temperature for 16 hours and concentrated under the reduced pressure to remove dimethylformamide. The concentrate was purified by column chromatography(ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 93%

m.p. : 88-89℃

^{1}H NMR ($CDCl_3$): δ 2.93(4H,t), 3.17(3H,s), 3.34(4H,t), 3.72(6H,s), 4.15(3H,t), 5.95(2H,s), 5.98(1H,s), 7.40(1H,t), 7.61(2H,m), 7.73(1H,s), 7.84(1H,d)

Mass(EI) m/z : Calcd for $C_{24}H_{28}N_4O_4$ 436.2110, found 436.2105

Example 99

1-[N-Ethyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl) piperazine(106mg, 0.25mmol) was dissolved in dimethylformamide(15ml) and was sodium hydride(6.0mg, 0.25mmol) was added and the solution was stirred at room temperature for 15 min. Iodoethane(35mg,

0.25mmol) was added to the above solution. The mixture was stirred at room temperature for 16hours and concentrated under the reduced pressure to remove dimethylformamide. The concentrate was purified by column chromatography(ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 91%

m.p. : 118-120℃

^{1}H NMR ($CDCl_3$): δ 1.16(3H,t), 2.89(4H,t), 3.30(4H,t), 3.63(2H,m), 3.71(6H,s), 4.13(3H,s), 5.93(2H,s), 5.98(1H,s), 7.41(1H,t), 7.60(1H,t), 7.66(1H,d), 7.71(1H,s), 7.84(1H,d)

Mass(EI) m/z : Calcd for $C_{25}H_{30}N_4O_4$ 450.2227, found 450.2206

Example 100

1-[N-Isopropyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)phenyl:

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl) piperazine(106mg, 0.25mmol) was dissolved in dimethylformamide(15ml) and sodium hydride(6.0mg, 0.25mmol) was added and the reaction solution was stirred at room temperature for 15 min.

2-Propyliodide(42mg, 0.25mmol) was added to the above solution. The mixture was stirred at room temperature for 16 hours and concentrated under the reduced pressure to remove the dimethylformamide. The concentrate was purified by column chromatography(ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 87%

m.p. : 123-125℃

^{1}H NMR ($CDCl_3$): δ 1.21(6H,d), 2.79(4H,t), 3.29(4H,t), 3.70(6H,s), 4.08(3H,s), 4.41(1H,m), 5.90(2H,s), 5.96(1H,s), 7.43(1H,t), 7.63(1H,t), 7.69(1H,d), 7.75(1H,s), 7.83(1H,d)

Example 101

1-[N-Cyclopropylmethyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl) piperazine(106mg, 0.25mmol) was dissolved in dimethylformamide(15ml) and sodium hydride(6.2mg, 0.26mmol) was added and the solution was

stirred at room temperature for 15 min. Bromomethylcyclopropane(22mg, 0.26mmol) was added to the above solution. The mixture was stirred at room temperature for 16 hours and concentrated under the reduced pressure to remove dimethylformamide. The concentrate was purified by column chromatography(ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 78%

m.p. : 118-120℃

^{1}H NMR ($CDCl_3$): δ 0.41(2H,m), 0.85(2H,m), 1.28(1H,m), 2.88(4H,t), 3.24(4H,t), 3.42(2H,d), 3.71(6H,s), 4.13(3H,s), 5.94(3H,s), 7.44(1H,d), 7.62(1H,d), 7.78(3H,m)

Example 102

1-[N-Benzyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl) piperazine(114mg, 0.27mmol) was dissolved in dimethylformamide(15ml) and sodium hydride(6.6mg, 0.27mmol) was added and the solution was stirred at room temperature for 15 min. Benzylbromide(46mg, 0.27mmol) was added to the above solution. The mixture was stirred at room temperature for 16 hours and concentrated under the reduced pressure to remove dimethylformamide. The concentrate was purified by column chromatography(ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 90%

m.p. : oil phase

^{1}H NMR ($CDCl_3$): δ 2.92(4H,t), 3.39(4H,t), 3.72(6H,s), 4.13(3H,s), 4.79(2H,s), 6.01(3H,m), 7.21(1H,m), 7.25(2H,m), 7.33(3H,m), 7.51(1H,s), 7.57(2H,m), 7.81(2H,d)

Example 103

1-[N-(2-Methoxyquinolin-3-yl)-N-methylaminocarbonyl]-4-(3,5-dimethyl phenyl)piperazine:

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl) piperazine was reacted by the same way with the example 98 to obtain the titled compound.

yield : 92%

m.p : 142-143℃

^{1}H NMR ($CDCl_3$): δ 2.27(6H,d), 2.90(4H,t), 3.17(3H,s), 3.34(4H,t), 4.15(3H,s), 6.41(2H,s), 6.49(1H,s), 7.40(1H,t), 7.63(1H,t), 7.65(1H,d), 7.73(1H,s), 7.84(1H,d)

Mass(EI) m/z : Calcd for $C_{24}H_{28}N_4O_2$ 404.2212, found 404.2225

Example 104

1-[N-Ethyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethyl phenyl)piperazine:

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl) piperazine was reacted by the same way with the example 99 to obtain the titled compound.

yield : 89%

m.p. : 84-86℃

^{1}H NMR ($CDCl_3$): δ 1.16(3H,t), 2.21(6H,s), 2.87(4H,t), 3.30(4H,t), 3.64(2H,q), 4.13(3H,t), 6.40(2H,s), 6.48(1H,s), 7.40(1H,t), 7.62(1H,t), 7.66(1H,d), 7.71(1H,s), 7.84(1H,d)

Example 105

1-[N-Isopropyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl) piperazine was reacted by the same way with the example 100 to obtain the titled compound.

yield : 84%

m.p. : 114-115℃

^{1}H NMR ($CDCl_3$): δ 1.21(6H,d), 2.20(6H,s), 2.77(4H,t), 3.28(4H,t), 4.08(3H,s), 4.39(1H,m), 6.37(2H,s), 6.46(1H,s), 7.41(1H,t), 7.63(1H,t), 7.69(1H,d), 7.75(1H,s), 7.83(1H,d)

Example 106

1-[N-Benzyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl) piperazine was reacted by the same way with the example 102 to

obtain the titled compound.
yield : 90%
m.p. : oil phase
^{1}H NMR ($CDCl_3$): δ 2.24(6H,s), 2.87(4H,t), 3.31(4H,t), 4.13(3H,s), 4.80(2H,s), 6.42(3H,s), 7.49(1H,t), 7.62(2H,m), 7.72(2H,m)

Example 107
1-[N-(2-Methoxyquinolin-3-yl)-N-methylaminocarbonyl]-4-(3-isopropoxyphenyl)piperazine:
1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3-isopropoxyphenyl) piperazine was reacted by the same way with the example 98 to obtain the titled compound.
yield : 92%
m.p. : oil phase
^{1}H NMR ($CDCl_3$): δ 1.28(6H,d), 2.97(4H,t), 3.18(3H,s), 3.37(4H,t), 4.14(3H,s), 4.49(1H,m), 6.41(3H,m), 7.13(1H,m), 7.40(1H,t), 7.62(1H,t), 7.66(1H,d), 7.74(1H,s), 7.84(1H,d)

Example 108
1-[N-Ethyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3-isopropoxyphenyl)piperazine:
1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3-isopropoxyphenyl) piperazine was reacted by the same way with the example 99 to obtain the titled compound.
yield : 87%
m.p. : oil phase
^{1}H NMR ($CDCl_3$): δ 1.16(3H,t), 1.34(6H,d), 2.89(4H,t), 3.30(4H,t), 3.63(2H,m), 4.13(3H,s), 4.55(1H,m), 6.49(2H,s), 7.05(1H,s), 7.20(1H,t), 7.32(1H,s), 7.37(1H,t), 7.50(1H,t), 7.70(1H,d), 7.77(1H,d), 8.80(1H,s)

Example 109
1-[(2-Methoxyquinolin-3-yl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl) piperazine:
Phenyl N-(2-methoxyquinolin-3-yl)thiocarbamate(56mg, 0.5mmol) and 1-(3,5-dimethoxyphenyl)piperazine(111mg, 0.5mmol) were dissolved in anhydrous tetrahydrofuran and DBU(117mg, 0.75mmol) was added. The

reaction solution was stirred at room temperature for 2 hours. The above solution was concentrated under the reduced pressure to remove tetrahydrofuran and concentrated was purified by column chromatography(Hexane : ether = 5:1) to obtain the titled compound.

yield : 76%

m.p. : 171-172℃

^{1}H NMR ($CDCl_3$): δ 3.41(4H,t), 3.81(6H,s), 4.17(3H,s), 4.21(4H,t), 6.12(1H,s), 6.20(1H,d), 7.38(1H,t), 7.54(1H,t), 7.74(1H,d), 7.81(1H,d), 8.96(1H,s)

Example 110

1-[(2-Methoxyquinolin-3-yl)aminothiocarbonyl]-4-(3,5-dimethylphenyl) piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)thiocarbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 109 to obtain the titled compound.

yield : 79%

m.p. : 170-171℃

^{1}H NMR ($CDCl_3$): δ 2.30(6H,s), 3.38(4H,t), 4.09(3H,s), 4.17(4H,t), 6.63(3H,m), 7.38(1H,t), 7.54(1H,t), 7.72(1H,d), 7.81(1H,d), 8.96(1H,s)

Example 111

1-[(2-Methoxyquinolin-3-yl)aminothiocarbonyl]-4-(3,5-difluorophenyl) piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)thiocarbamate and 1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 109 to obtain the titled compound.

yield : 78%

m.p. : 140-142℃

^{1}H NMR ($CDCl_3$): δ 3.44(4H,t), 4.20(4H,t), 4.25(3H,s), 6.33(2H,m), 6.45(1H,d), 7.41(1H,t), 7.56(1H,m), 7.72(1H,m), 7.97(1H,m), 8.96(1H,s)

Example 112

1-[(2-Methoxyquinolin-3-yl)aminothiocarbonyl]-4-(3,5-dichlorophenyl) piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)thiocarbamate and

1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 109 to obtain the titled compound.
yield : 62%
m.p.: 181-183℃
^{1}H NMR ($CDCl_3$): δ 3.44(4H,t), 4.20(4H,t), 4.26(3H,s), 6.77(1H,s), 6.88(2H,t), 7.41(1H,t), 7.59(1H,t), 7.70(2H,m), 8.01(1H,t), 8.11(1H,s), 8.93(1H,s)

Example 113
1-[(2-Methoxyquinolin-3-yl)aminothiocarbonyl]-4-(3-methoxyphenyl) piperazine:
Phenyl N-(2-methoxyquinolin-3-yl)thiocarbamate and 1-(3-methoxyphenyl)piperazine were reacted by the same way with the example 109 to obtain the titled compound.
yield : 81%
m.p. : oil phase
^{1}H NMR ($CDCl_3$): δ 3.17(4H,t), 3.89(3H,s), 4.17(4H,t), 6.90(4H,m), 7.34(1H,t), 7.48(1H,t), 7.70(1H,d), 7.77(1H,d), 8.80(1H,s)

Example 114
1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl) piperazine:

a) Phenyl N-(2-methylquinolin-3-yl)carbamate:
3-amino-2-methylquinoline(4g, 25mmol) and phenyl chloroformate(4.04g, 25mmol) were dissolved in methylene chloride and then was stirred at room temperature for 2 hrs. The mixture solution was concentrated under the reduced pressure to remove methylene chloride and purified by column chromatography(ethylacetate : hexane = 1:10) to obtain the titled compound.
yield : 88%
^{1}H NMR ($CDCl_3$): δ 2.77(3H,s), 7.30-7.53(9H,m), 8.67(1H,s)

b) 1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl) piperazine:
Phenyl N-(2-methylquinolin-3-yl)carbamate(140mg, 0.5mmol) and

1-(3,5-dimethoxyphenyl)piperazine(112mg, 0.5mmol) were dissolved in tetrahydrofuran and DBU(117mg, 0.75mmol) was added and then the mixture was stirred at room temperature for 2 hrs. The above solution was concentrated under the reduced pressure to remove tetrahydrofuran and purified by column chromatography(ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 84%

m.p. : 199-200℃

^{1}H NMR ($CDCl_3$): δ 2.81(3H,s), 3.30(4H,t), 3.76(4H,t), 3.80(6H,s), 6.08(1H,s), 6.12(2H,d), 7.48(1H,t), 7.62(1H,t), 7.71(1H,d), 8.03(1H,d), 8.59(1H,s)

Example 115

1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl) piperazine:

Phenyl N-(2-methylquinolin-3-yl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 114 to obtain the titled compound.

yield : 86%

m.p. : 230-232℃

^{1}H NMR ($CDCl_3$): δ 2.31(6H,s), 2.82(3H,s), 3.29(4H,t), 3.76(4H,t), 6.60(3H,s), 7.49(1H,t), 7.63(1H,t), 7.73(1H,d), 8.05(1H,d), 8.61(1H,s)

Example 116

1-[(2-methylquinolin-3-yl)aminocarbonyl]-4-(2,3-dimethylphenyl) piperazine:

Phenyl N-(2-methylquinolin-3-yl)carbamate and 1-(2,3-dimethylphenyl)piperazine were reacted by the same way with the example 114 to obtain the titled compound.

yield : 81%

m.p. : 169-170℃

^{1}H NMR ($CDCl_3$): δ 2.28(6H,d), 2.84(3H,s), 3.00(4H,t), 3.76(4H,t), 6.94(2H,m), 7.11(1H,t), 7.49(1H,t), 7.63(1H,t), 7.72(1H,d), 8.07(1H,d), 8.64(1H,s)

Example 117

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-difluorophenyl) piperazine:

Phenyl N-(2-methylquinolin-3-yl)carbamate and 1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 114 to obtain the titled compound.

yield : 81%

m.p. : 238-240℃

^{1}H NMR ($CDCl_3$): δ 2.81(3H,t), 3.34(4H,t), 3.77(4H,t), 6.32(1H,t), 6.39(2H,d), 7.49(1H,t), 7.63(1H,t), 7.72(1H,d), 8.03(1H,d), 8.58(1H,s)

Example 118

1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(3,5-dichlorophenyl) piperazine:

Phenyl N-(2-methylquinolin-3-yl)carbamate and 1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 114 to obtain the titled compound.

yield : 65%

m.p. : 247-249℃

^{1}H NMR ($CDCl_3$): δ 2.79(3H,s), 3.33(4H,t), 3.75(4H,t), 6.78(2H,s), 6.87(1H,s), 7.49(1H,t), 7.63(1H,t), 7.72(1H,d), 8.56(1H,s)

Example 119

1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl) piperazine:

Phenyl N-(2-methylquinolin-3-yl)carbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 114 to obtain the titled compound.

yield : 83%

m.p. : 135-136℃

^{1}H NMR ($CDCl_3$): δ 2.82(3H,s), 3.18(4H,t), 3.79(4H,t), 3.91(3H,s), 6.88(1H,d), 6.97(2H,s), 7.07(1H,m), 7.48(1H,t), 7.62(1H,t), 7.72(1H,d), 8.04(1H,d), 8.63(1H,s)

Example 120

1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(2-fluorophenyl)piperazine:

Phenyl N-(2-methylquinolin-3-yl)carbamate and 1-(2-fluorophenyl)piperazine were reacted by the same way with the example 114 to obtain the titled compound.

yield : 84%

m.p. : 201-203℃

^{1}H NMR ($CDCl_3$): δ 2.84(3H,s), 3.20(4H,t), 3.80(4H,t), 6.99(2H,m), 7.07(2H,m), 7.49(1H,t), 7.62(1H,t), 7.71(1H,d), 8.04(1H,d), 8.62(1H,s)

Example 121

1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(2-chlorophenyl)piperazine:

Phenyl N-(2-methylquinolin-3-yl)carbamate and 1-(2-chlorophenyl)piperazine were reacted by the same way with the example 114 to obtain the titled compound.

yield : 72%

m.p. : 180-181℃

^{1}H NMR ($CDCl_3$): δ 2.83(3H,s), 3.16(4H,t), 3.80(4H,t), 7.04(3H,m), 7.40(1H,d), 7.49(1H,t), 7.63(1H,t), 7.71(1H,d), 8.05(1H,d), 8.62(1H,s)

Example 122

1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(2-methylthiophenyl) piperazine:

Phenyl N-(2-methylquinolin-3-yl)carbamate and 1-(2-methylthiophenyl)piperazine were reacted by the same way with the example 114 to obtain the titled compound.

yield : 76%

m.p. : 165-166℃

^{1}H NMR ($CDCl_3$): δ 2.45(3H,s), 2.85(3H,s), 3.11(4H,t), 3.79(4H,t), 7.05(1H,m), 7.15(3H,d), 7.49(1H,t), 7.63(1H,t), 7.69(1H,d), 8.07(1H,d), 8.62(1H,s)

Example 123

1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(2-methoxy-5-methyl phenyl)piperazine:

Phenyl N-(2-methylquinolin-3-yl)carbamate and 1-(2-methoxy-5-methylphenyl)piperazine were reacted by the same way with the example 114 to obtain the titled compound.

yield : 80%

m.p. : oil phase

^{1}H NMR ($CDCl_3$): δ 2.30(3H,s), 2.72(3H,s), 3.17(4H,t), 3.70(4H,t), 3.87(3H,s), 6.77(1H,s), 6.82(2H,s), 7.73(4H,m), 8.60(1H,s)

Example 124

1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(1-naphthyl)piperazine:

Phenyl N-(2-methylquinolin-3-yl)carbamate and 1-(1-naphthyl)piperazine were reacted by the same way with the example 114 to obtain the titled compound.

yield : 64%

m.p. : 220-222℃

^{1}H NMR ($CDCl_3$): δ 2.83(3H,s), 3.23(4H,t), 3.80(4H,t), 6.91(1H,s), 7.12(1H,d), 7.44(1H,d), 7.50(3H,m), 7.61(2H,m), 7.73(1H,d), 7.86(1H,d), 8.05(1H,d), 8.23(1H,d), 8.64(1H,s)

Example 125

1-[(2-Methylquinolin-3-yl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl) piperazine:

a) Phenyl N-(2-methylquinolin-3-yl)thiocarbamate:

3-Amino-2-methylquinoline(4g, 25mmol) and phenyl chlorothionoformate(4.32g, 25mmol) were dissolved in methylene chloride and then was stirred at room temperature for 2hours. The mixture solution was concentrated under reduced pressure to remove methylene chloride and purified by column chromatography(ethylacetate : hexane = 1 : 2) to obtain the titled compound.

yield : 78%

^{1}H NMR ($CDCl_3$): δ 2.77(3H,s), 7.09-7.90(9H,m), 9.14(1H,s)

b)

1-[(2-Methylquinolin-3-yl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl) piperazine:

Phenyl N-(2-methylquinolin-3-yl)thiocarbamate(147mg, 0.5mmol) and 1-(3,5-dimethoxyphenyl)piperazine(112mg, 0.5mmol) were dissolved in anhydrous tetrahydrofuran and DBU(117mg, 0.75mmol) was added and

then the mixture was stirred at room temperature for 2 hrs. The above solution was concentrated under the reduced pressure to remove tetrahydrofuran and purified by column chromatography(ethylacetate : hexane = 1 : 2) to obtain the titled compound.

yield : 86%

m.p. : 211-212℃

^{1}H NMR ($CDCl_3$): δ 2.81(3H,s), 3.35(4H,t), 3.79(6H,s), 4.14(4H,t), 6.07(3H,s), 7.49(2H,t), 7.68(2H,m), 8.01(1H,s), 8.07(1H,d)

Example 126

1-[(2-Methylquinolin-3-yl)aminothiocarbonyl]-4-(3,5-dimethylphenyl) piperazine:

Phenyl N-(2-methylquinolin-3-yl)thiocarbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 125 to obtain the titled compound.

yield : 81%

m.p. : 196-197℃

^{1}H NMR ($CDCl_3$): δ 2.27(6H,s), 2.81(3H,s), 3.31(4H,t), 4.11(4H,t), 6.53(2H,s), 6.58(1H,s), 7.48(2H,t), 7.67(2H,m), 7.96(1H,s), 8.04(1H,d)

Example 127

1-[(2-Methylquinolin-3-yl)aminothiocarbonyl]-4-(3,5-difluorophenyl) piperazine:

Phenyl N-(2-methylquinolin-3-yl)thiocarbamate and 1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 125 to obtain the titled compound.

yield : 74%

m.p. : 211-213℃

^{1}H NMR ($CDCl_3$): δ 2.85(3H,s), 3.43(4H,t), 4.22(4H,t), 6.33(2H,m), 7.49(1H,t), 7.64(1H,d), 7.72(1H,t), 8.16(2H,m)

Example 128

1-{[2-(Pyridin-2-yl)quinolin-4-yl]aminocarbonyl}-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-[2-(pyridin-3-yl)quinolin-4-yl]carbamate(171mg, 0.5mmol) and 1-(3,5-dimethoxyphenyl)piperazine(111mg, 0.5mmol) were dissolved in

anhydrous tetrahydrofuran and DBU(117mg, 0.75mmol) was added and then the mixture was stirred at room temperature for 2hrs. The above solution was concentrated under the reduced pressure to remove tetrahydrofuran and purified by column chromatography (dichloromethane : methanol=20:1) to obtain the titled compound.
yield : 73%
m.p. : 97-98℃
^{1}H NMR ($CDCl_3$): δ 3.34(4H,t), 3.79(6H,s), 3.90(4H,t), 6.07(1H,s), 6.12(2H,s), 7.43(1H,t), 7.50(1H,t), 7.68(1H,t), 7.93(1H,t), 8.26(1H,d), 8.59(1H,d), 8.80(1H,d), 8.98(1H,s)
Mass(EI) m/z : Calcd for $C_{31}H_{27}N_5O_3$ 517.2113, found 517.3244

Example 129
1-{[2-(Pyridin-3-yl)quinolin-4-yl]aminocarbonyl}-4-(3,5-dimethoxyphenyl)piperazine:
Phenyl N-[2-pyridin-3-yl)quinolin-4-yl]carbamate(171mg, 0.5mmol) and 1-(3,5-dimethoxyphenyl)piperazine(111mg, 0.5mmol) were dissolved in anhydrous tetrahydrofuran and DBU(117mg, 0.75mmol) was added and then the mixture was stirred at room temperature for 2 hours. The above solution was concentrated under the reduced pressure to remove tetrahydrofuran and purified by column chromatography (dichloromethane : methanol = 20:1) to obtain the titled compound.
yield : 67%
m.p. : 95-96℃
^{1}H NMR ($CDCl_3$): δ 3.36(4H,t), 3.87(6H,s), 3.90(4H,t), 6.08(1H,s), 6.12(2H,s), 7.50(1H,t), 7.71(1H,t), 7.93(1H,t), 8.25(1H,d), 8.53(1H,d), 8.67(1H,s), 8.73(1H,d), 9.35(1H,s)

Example 130
1-{[2-Thien-2-yl)quinolin-4-yl]aminocarbonyl}-4-(3,5-dimethoxyphenyl) piperazine:
Phenyl N-[2-(thien-2-yl)quinolin-4-yl]carbamate(173mg, 0.5mmol) and 1-(3,5-dimethoxyphenyl)piperazine(111mg, 0.5mmol) were dissolved in anhydrous tetrahydrofuran and DBU(117mg, 0.75mmol) was added. The resulting mixture was stirred at room temperature for 2 hours, concentrated under the reduced pressure to remove tetrahydrofuran and

purified by column chromatography(ethylaetate : hexane = 1:1) to obtain the titled compound.
yield : 61%
m.p. : oil phase
^{1}H NMR ($CDCl_3$): δ 3.37(4H,t), 3.59(6H,s), 3.97(4H,t), 7.01(3H,m), 7.49(1H,t), 7.69(1H,t), 7.93(1H,t), 8.20(1H,d), 8.52(1H,d), 8.64(1H,s), 8.71(1H,d), 9.35(1H,s)

Example 131
1-([2-(Pyridin-3-yl)quinolin-4-yl]aminocarbonyl)-4-(3,5-dimethylphenyl) piperazine:
Phenyl N-[2-(pyridin-3-yl)quinolin-4-yl]carbamate(171mg, 0.5mmol) and 1-(3,5-dimethylphenyl)piperazine(95mg, 0.5mmol) were dissolved in anhydrous tetrahydrofuran and DBU(117mg, 0.75mmol) was added. The resulting mixture was stirred at room temperature for 2 hours, concentrated under the reduced pressure to remove tetrahydrofuran, and purified by column chromatography(ethylacetate : hexane =1:1) to obtain the titled compound.
yield : 64%
m.p. : 211-213℃
^{1}H NMR ($CDCl_3$): δ 2.31(6H,s), 3.32(4H,t), 3.85(4H,t), 6.61(3H,s), 7.47(1H,t), 7.55(1H,t), 7.72(1H,t), 7.86(1H,t), 8.25(1H,d), 8.53(1H,d), 8.66(1H,s), 8.72(1H,d), 9.37(1H,s)

Example 132
1-[N-(5,6-Dimethyl-2-methoxypyridin-3-yl)-N-methylaminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(100mg, 0.25mmol) was dissolved in dimethylformamide(15ml) and thereto sodium hydride(6.0mg, 0.25mmol) was added. The resulting mixture was stirred at room temperature for 15 min and thereto iodomethane(35mg, 0.25mmol) was added. The resulting mixture was stirred at room temperature for 16 hrs, concentrated under the reduced presssure to remove dimethylformamide, and purified by column chromatography(ethylacetate : hexane=1:2) to obtain the titled compound.

yield : 94%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 2.17(3H,s), 2.38(3H,s), 2.92(4H,t), 3.04(3H,s), 3.29(4H,t), 3.74(6H,s), 3.96(3H,s), 6.00(3H,m), 7.08(1H,s)

Example 133

1-[N-Ethyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(100mg, 0.25mmol) was dissolved in dimethylformamide(15ml) and thereto sodium hydride(6.0mg, 0.25mmol) was added, followed by stirring at room temperature for 15 min and then iodoethane(39.2mg, 0.25mmol) was added. The resulting mixture was stirred at room temperature for 16 hrs, concentrated under the reduced pressure to remove dimethylformamide, and purified by column chromatography(ethylacetate : hexane=1:2) to obtain the titled compound.

yield : 86%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 1.08(3H,t), 2.04(3H,s), 2.38(3H,s), 2.90(4H,t), 3.26(4H,t), 3.52(2H,q), 3.74(6H,s), 5.99(3H,m), 7.06(1H,s)

Example 134

1-[N-Isopropyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(100mg, 0.25mmol) was dissolved in dimethylformamide(15ml) and thereto sodium hydride(6.0mg, 0.25mmol) was added, followed by stirring at room temperature for 15 min, and then 2-iodopropane(42mg, 0.25mmol) was added. The resulting mixture was stirred at room temperature for 16 hrs, concentrated under the reduced pressure to remove dimethylformamide, purified by column chromatography(ethylacetate : hexane=1:2) to obtain the titled compound.

yield : 78%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 1.13(6H,d), 2.19(3H,s), 2.38(3H,s), 2.82(4H,t), 3.26(4H,t), 3.74(6H,s), 3.89(3H,s), 4.27(1H,m), 6.06(1H,s), 6.10(2H,d),

7.07(1H,s), 8.14(1H,s)
Mass(EI) m/z : Calcd for $C_{24}H_{34}N_4O_4$ 442.2580, found 442.2538

Example 135

1-[N-(5,6-Dimethyl-2-methoxypyridin-3-yl)-N-methylaminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3,5-dimethyl phenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 97%
m.p. : oil phase
^{1}H NMR($CDCl_3$) δ : 2.15(6H,s), 2.23(3H,s), 2.37(3H,s), 2.89(4H,t), 3.04(3H,s), 3.30(4H,t), 3.97(3H,s), 6.46(3H,m), 7.08(1H,s)

Example 136

1-[N-(5,6-Dimethyl-2-methoxypyridin-3-yl)-N-methylaminocarbonyl]-4-(2-methoxyphenyl)piperazine:

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxyph enyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 94%
m.p. : 131-132°C
^{1}H NMR($CDCl_3$) δ : 2.16(3H,s), 2.38(3H,s), 2.80(4H,t), 3.05(3H,s), 3.35(4H,t), 3.82(3H,s), 3.97(3H,s), 6.83(4H,m), 7.08(1H,s)

Example 137

1-[N-Ethyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxyph enyl)piperazine was reacted by the same way with the example 133 to obtain the titled compound.

yield : 87%
m.p. : 112-113°C
^{1}H NMR($CDCl_3$) δ : 1.08(3H,t), 2.16(3H,s), 2.38(3H,s), 2.77(4H,t), 3.31(4H,t), 3.58(2H,q), 3.81(3H,s), 3.96(3H,s), 6.88(4H,m), 7.06(1H,s)

Example 138

1-[N-Benzyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine(100mg, 0.27mmol) was dissolved in dimethylformamide(15ml) and thereto sodium hydride(6.5mg, 0.27mmol) was added, followed by stirring at room temperature for 1hr, and successively benzyl bromide(46.2mg, 0.27mmol) was added. The resulting mixture was stirred at room temperature for 16 hrs, concentrated under the reduced pressure and purified by column chromatography(ethylacetate : hexane = 1: 2) to obtain the titled compound.

yield : 93%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 2.08(3H,s), 2.35(3H,s), 2.85(4H,t), 3.32(4H,t), 3.81(3H,s), 3.96(3H,s), 4.76(2H,s), 6.96(4H,m), 7.41(5H,m)

Example 139

1-[N-Cyclopropylmethyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl) aminocarbonyl]-4-(2-methoxyphenyl)piperazine:

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine(100mg, 0.26mmol) was dissolved in dimethylformamide(15ml) and thereto sodium hydride(6.2mg, 0.26mmol) was added, followed by stirring at room temperature for 15 min, and successively bromomethylcyclopropane(21.8mg, 0.26mmol) was added. The resulting mixture was stirred at room temperature for 16 hrs, concentrated under the reduced pressure and purified by column chromatography(ethylacetate : hexane = 1: 2) to obtain the titled compound.

yield : 78%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 0.34(2H,m), 0.49(2H,m), 1.35(1H,m), 2.85(4H,t), 3.28(4H,t), 3.40(2H,s), 3.89(3H,s), 3.97(3H,s), 6.97(4H,m), 7.11(1H,s)

Example 140

1-[N-(5,6-Dimethyl-2-methoxypyridin-3-yl)-N-methylaminocarbonyl]-4-

(5-methoxy-2-methylphenyl)piperazine:
1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(5-methoxy-2-methylphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.
yield : 74%
m.p. : 91-93°C
^{1}H NMR($CDCl_3$) δ : 2.15(3H,s), 2.18(3H,s), 2.39(3H,s), 2.67(4H,t), 3.05(3H,s), 3.30(4H,t), 3.75(3H,s), 3.97(3H,s), 6.48(3H,m), 7.10(1H,s)

Example 141
1-[N-Ethyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(5-methoxy-2-methylphenyl)piperazine:
1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(5-methoxy-2-methylphenyl)piperazine was reacted by the same way with the example 133 to obtain the titled compound.
yield : 94%
m.p. : oil phase
^{1}H NMR($CDCl_3$) δ : 1.09(3H,t), 2.15(3H,s), 2.18(3H,s), 2.39(3H,s), 2.60(4H,t), 3.27(4H,t), 3.59(2H,q), 3.75(3H,s), 3.96(3H,s), 6.45(3H,m), 7.08(1H,s)

Example 142
1-[N-Benzyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(5-methoxy-2-methylphenyl)piperazine:
1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(5-methoxy-2-methylphenyl)piperazine was reacted by the same way with the example 138 to obtain the titled compound.
yield : 97%
m.p. : oil phase
^{1}H NMR($CDCl_3$) δ : 1.25(3H,t), 2.08(3H,s), 2.14(3H,s), 2.35(3H,s), 2.60(4H,t), 3.32(4H,t), 3.74(3H,s), 3.95(3H,s), 4.66(2H,s), 6.44(4H,m), 6.96(5H,m), 7.12(1H,s)

Example 143
1-[N-(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 87%

m.p. : 78-79℃

^{1}H NMR($CDCl_3$) δ : 1.14(3H,t), 2.41(3H,s), 2.52(2H,q), 2.91(4H,t), 3.02(3H,s), 3.28(4H,t), 3.74(6H,s), 3.98(3H,s), 5.98(3H,m), 7.11(1H,s)

Mass(EI) m/z : Calcd for $C_{23}H_{32}N_4O_4$ 428.2423, found 428.2434

Example 144

1-[N-(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 84%

m.p. : 86-87℃

^{1}H NMR($CDCl_3$) δ : 1.14(3H,t), 2.23(6H,s), 2.45(3H,s), 2.58(2H,q), 2.87(4H,t), 3.05(3H,s), 3.30(4H,t), 3.98(3H,s), 6.46(3H,m), 7.11(1H,s)

Mass(EI) m/z : Calcd for $C_{23}H_{32}N_4O_2$ 396.2525, found 396.2575

Example 145

1-[N-Ethyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 133 to obtain the titled compound.

yield : 86%

m.p. : 84-85℃

^{1}H NMR($CDCl_3$) δ : 1.13(6H,m), 2.23(6H,s), 2.41(3H,s), 2.58(2H,q), 2.85(4H,t), 3.26(4H,t), 3.46(2H,q), 3.96(3H,s), 6.45(3H,m), 7.08(1H,s)

Example 146

1-[N-(2-Methoxy-6-methyl-5-propylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(2-Methoxy-6-methyl-5-propylpyridin-3-yl)aminocarbonyl]-4-

(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 89%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 1.01(3H,t), 1.78(2H,m), 2.21(3H,s), 2.78(2H,t), 3.78(6H,s), 3.86(4H,t), 3.99(3H,s), 4.00(3H,s), 4.22(4H,t), 6.01(3H,m), 7.02(1H,s)

Example 147

1-[N-(6-Ethyl-2-methoxy-5-methylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(6-Ethyl-2-methoxy-5-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 85%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 2.21(3H,t), 2.21(3H,s), 2.45(2H,q), 3.21(4H,t), 3.40(3H,s), 3.67(4H,t), 3.77(6H,s), 4.01(3H,s), 6.07(3H,m), 6.96(1H,s), 8.07(1H,s)

Example 148

1-[N-(2-Methoxy-5-methyl-6-propylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(2-Methoxy-5-methyl-6-propylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 86%

m.p. : 106-107℃

^{1}H NMR($CDCl_3$) δ : 0.98(3H,t), 1.73(2H,q), 2.18(3H,s), 2.63(2H,t), 2.92(4H,t), 3.05(3H,s), 3.29(4H,t), 3.74(6H,s), 3.96(3H,s), 6.00(3H,m), 7.11(1H,s)

Mass(EI) m/z : Calcd for $C_{24}H_{34}N_4O_4$ 442.2580, found 442.2543

Example 149

1-[N-(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 89%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 2.50(3H,s), 2.70(3H,s), 2.97(4H,t), 3.09(3H,s), 3.33(4H,t), 3.75(6H,s), 4.06(3H,s), 6.03(3H,m), 7.72(1H,s)

Mass(EI) m/z : Calcd for $C_{23}H_{30}N_4O_5$ 442.2216, 442.2229

Example 150

1-[N-Ethyl-N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 133 to obtain the titled compound.

yield : 87%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 1.09(3H,t), 2.49(3H,s), 2.70(3H,s), 3.00(4H,t), 3.32(4H,t), 3.77(6H,s), 4.01(3H,s), 4.09(2H,q), 5.98(3H,m), 7.76(1H,s)

Example 151

1-[N-(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same with the example 132 to obtain the titled compound.

yield : 88%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 2.24(6H,s), 2.50(3H,s), 2.70(3H,s), 2.93(4H,t), 3.09(3H,s), 3.28(4H,t), 4.06(3H,s), 6.46(3H,m), 7.73(1H,s)

Example 152

1-(N-[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]-N-methyl aminocarbonyl)-4-(3,5-dimethoxyphenyl)piperazine:

1-[N-(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine(0.47mmol) was dissolved in

anhydrous ethanol(15ml) and thereto sodium borohydride(17.3mg) was added, then followed by stirring at room temperature for 2 hrs. The resulting mixture was concentrated under the reduced pressure to remove ethanol and purified by column chromatography(ethylacetate : hexane = 2:1) to obtain the titled compound.

yield : 97%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 1.14(3H,d), 2.44(3H,s), 2.93(4H,t), 3.06(3H,s), 3.30(4H,t), 3.74(6H,s), 3.98(3H,s), 5.03(1H,q), 6.02(3H,m), 7.50(1H,s)

Example 153

1-(N-Ethyl-N-[5-(1-hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl] aminocarbonyl)-4-(3,5-dimethoxyphenyl)piperazine;

1-[N-Ethyl-N-(5-cetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl] -4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 152 to obtain the titled compound.

yield : 96%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 1.09(3H,t), 1.41(3H,d), 2.44(3H,s), 2.91(4H,t), 3.27(4H,t), 3.54(1H,q), 3.74(6H,s), 3.96(3H,s), 5.03(1H,q), 6.02(3H,m), 8.46(1H,s)

Example 154

1-(N-[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]-N-methylaminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[N-Methyl-N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)amino carbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 152 to obtain the titled compound.

yield : 97%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 1.41(3H,d), 2.24(6H,s), 2.44(3H,s), 2.91(4H,t), 3.06(3H,s), 3.26(4H,t), 3.99(3H,s), 5.03(1H,q), 6.49(3H,m), 7.50(1H,s)

Example 155

1-(N-[5-(1-Hydroxy-1-methylethyl)-2-methoxy-6-methylpyridin-3-yl]-N-methylaminocarbonyl)-4-(3,5-dimethoxyphenyl)piperazine:

1-[N-Methyl-N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)amino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine(221mg, 0.5mmol) was dissolved in tetrahydrofuran(10ml) and thereto methyl magnesium bromide(0.50ml, 1.50mmol). The resulting mixture was refluxed for 15 hrs, concentrated under the reduced pressure to remove used solvent, extracted with ethylacetate, filtered to dryness, and purified by column chromatography(ethylacetate : hexane =1:2) to obtain the titled compound.

yield : 92%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 1.59(6H,s), 2.66(3H,s), 2.93(4H,t), 3.06(3H,s), 3.30(4H,t), 3.74(6H,s), 3.99(3H,s), 6.03(3H,m), 7.45(1H,s)

Example 156

1-{N-[5-(1-Hydroxy-1-methylpropyl)-2-methoxy-6-methylpyridin-3-yl] -N-methylaminocarbonyl}-4-(3,5-dimethylphenyl)piperazine:

1-[N-Methyl-N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)amino carbonyl]-4-(3,5-dimethylphenyl)piperazine(213mg, 0.5mmol) was dissolved in tetrahydrofuran(10ml) and thereto methyl magnesium bromide(0.50ml, 1.50mmol) was added slowly, then refluxed for 15 hrs. The resulting mixture was concentrated under the reduced pressure to remove the used solvent, extracted with ethylacetate, filtered to dryness, and purified by column chromatography(ethylacetate : hexane =1:2) to obtain the titled compound.

yield : 88%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 0.79(3H,t), 1.58(3H,s), 1.85(2H,q), 2.61(3H,s), 2.99(4H,t), 3.07(3H,s), 3.30(4H,t), 3.76(6H,s), 6.12(3H,m), 7.47(1H,s)

Example 157

1-{N-[2-Methoxy-5-(1-methoxyethyl)-6-methylpyridin-3-yl]-N-methyl aminocarbonyl}-4-(3,5-dimethoxyphenyl)piperazine:

1-{N-[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]amino carbonyl}-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 95%

m.p. : 117-119℃
^{1}H NMR($CDCl_3$) δ : 1.34(3H,t), 2.43(3H,s), 2.94(4H,t), 3.06(3H,s), 3.18(3H,s), 3.30(4H,t), 3.74(6H,s), 3.99(3H,s), 4.44(1H,q), 6.02(3H,m), 7.37(1H,s)

Example 158
1-[N-(2-Methoxy-6-methyl-5-vinylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
1-[(2-Methoxy-6-methyl-5-vinylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.
yield : 94%
m.p. : oil phase
^{1}H NMR($CDCl_3$) δ : 2.46(3H,s), 2.93(4H,t), 3.07(3H,s), 3.30(4H,t), 3.73(6H,s), 3.99(3H,s), 5.25(1H,d), 5.48(1H,d), 6.01(3H,m), 6.78(1H,s), 7.43(1H,s)

Example 159
1-[N-(2-Methoxy-6-methyl-5-vinylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethylphenyl)piperazine:
1-[(2-Methoxy-6-methyl-5-vinylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.
yield : 89%
m.p. : oil phase
^{1}H NMR($CDCl_3$) δ : 2.24(6H,s), 2.43(3H,s), 2.90(4H,t), 3.04(3H,s), 3.27(4H,t), 3.99(3H,s), 5.23(1H,d), 5.45(1H,d), 6.05(3H,m), 6.77(1H,s), 7.40(1H,s)

Example 160
1-[N-Ethyl-N-(2-methoxy-6-methyl-5-vinylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
1-[(2-Methoxy-6-methyl-5-vinylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 133 to obtain the titled compound.
yield : 92%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 1.09(3H,t), 2.43(3H,s), 2.94(4H,t), 3.28(4H,t), 3.77(6H,s), 4.01(3H,s), 4.11(2H,q), 5.25(1H,d), 5.49(1H,d), 5.98(3H,m), 6.77(1H,s), 7.44(1H,s)

Example 161

1-[N-(5-Isopropenyl-2-methoxy-6-methylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(5-Isopropenyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 92%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 1.98(3H,s), 2.43(3H,s), 2.92(4H,t), 3.06(3H,s), 3.29(4H,t), 3.74(6H,s), 3.99(3H,s), 4.84(1H,s), 5.30(1H,s), 6.01(3H,m), 7.10(1H,s)

Example 162

1-[N-(5-Isopropenyl-2-methoxy-6-methylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(5-Isoprophenyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 91%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 1.98(3H,s), 2.24(6H,s), 2.43(3H,s), 2.90(4H,t), 3.06(3H,s), 3.28(4H,t), 4.00(3H,s), 4.84(1H,s), 5.19(1H,s), 6.46(3H,m), 7.10(1H,s)

Example 163

Ethyl 2-(([4-(3,5-dimethoxyphenyl)piperazino]carbonyl)(5-acetyl-2-methoxy-6-methylpyridin-3-yl)amino)acetate:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(200mg, 0.5mmol) was dissolved in dimethylformamide(15ml) and thereto sodium hydride(18.5mg, 0.5mmol) was added, then followed by stirring at room temperature for 15 min.

and ethylbromoacetate(83.5mg, 0.5mmol) was added. The resulting mixture was stirred at room temperature for 3 hrs, concentrated under the reduced pressure to remove the used solvent, and purified by column chromatography(ethylacetate : hexane =1:2) to obtain the titled compound.

yield : 84%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 1.26(3H,t), 2.51(3H,s), 2.69(3H,s), 3.04(4H,t), 3.43(4H,t), 3.75(6H,s), 4.05(3H,s), 4.15(2H,q), 4.19(2H,s), 6.08(3H,s), 7.96(1H,s)

Example 164

Ethyl 2-({[4-(3,5-dimethylphenyl)piperazino]carbonyl}(5-acetyl-2-methoxy-6-methylpyridin-3-yl)amino)acetate:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 163 to obtain the titled compound.

yield : 80%

m.p. : oil phase

^{1}H NMR($CDCl_3$) δ : 1.25(3H,t), 2.56(3H,s), 2.69(3H,s), 3.00(4H,t), 3.29(4H,t), 3.78(6H,s), 4.06(3H,s), 4.18(2H,s), 5.99(3H,m), 7.98(1H,s)

Example 165

2-({[4-(3,5-Dimethoxyphenyl)piperazino]carbonyl}(5-acetyl-2-methoxy-6-methylpyridin-3-yl)amino)acetic acid:

Ethyl ({[4-(3,5-dimethoxyphenyl)piperazino]carbonyl}(5-acetyl-2-methoxy-6-methylpyridin-3-yl)amino)acetate(200mg, 0.38mmol) was dissolved in mixed solvent of dioxane : distilled water =4:1(15ml), and lithium hydroxide hydrate(48.1mg, 1.14mmol) was added, then followed by stirring at room temperature for 3 hrs. The resulting mixture was made acidic with 1N-HCl, extracted with ethylacetate, filtered to dryness, concentrated under the reduced pressure and purified by column chromatography(ethylacetate : hexane = 1 : 2) to obtain the titled compound.

yield : 94%

m.p. : 135-137℃

^{1}H NMR($CDCl_3$) δ : 2.52(3H,s), 2.69(3H,s), 3.11(4H,t), 3.49(4H,t), 3.74(6H,s), 4.05(3H,s), 4.24(2H,s), 6.15(3H,m), 7.83(1H,s)

Example 166

Ethyl 2-({[4-(3,5-dimethoxyphenyl)piperazino]carbonyl}[5-(1-hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]amino)acetate:
Ethyl 2-({[4-(3,5-dimethoxyphenyl)piperazino]carbonyl}(5-acetyl-2-methoxy-6-methylpyridin-3-yl)amino)acetate was reacted by the same way with the example 152 to obtain the titled compound.
yield : 97%
m.p. : 125-127℃
^{1}H NMR($CDCl_3$) δ : 1.26(3H,t), 1.42(3H,d), 2.44(3H,s), 3.04(4H,t), 3.31(4H,t), 3.75(6H,s), 3.97(3H,s), 4.16(2H,q), 4.19(2H,s), 6.15(3H,m), 7.69(1H,s)

Example 167

Ethyl 2-({[4-(3,5-dimethoxyphenyl)piperazino]carbonyl}[5-(1-hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]amino)acetate:
Ethyl 2-({[4-(3,5-dimethoxyphenyl)piperazino]carbonyl}[5-(1-hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]amino)acetate was reacted by the same way with the example 164 to obtain the titled compound.
yield : 92%
m.p. : oil phase
^{1}H NMR($CDCl_3$) δ : 1.41(3H,d), 2.44(3H,s), 2.98(4H,t), 3.36(4H,t), 3.74(6H,s), 3.98(3H,s), 4.40(2H,s), 5.00(1H,q), 6.08(3H,m), 7.69(1H,s)

Example 168

Ethyl 2-({[4-(3,5-dimethylphenyl)piperazino]carbonyl}[5-(1-hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]amino)acetate:
Ethyl 2-({[4-(3,5-dimethylphenyl)piperazino]carbonyl}(5-acetyl-2-methoxy-6-methylpyridin-3-yl)amino)acetate was reacted by the same way with the example 152 to obtain the titled compound.
yield : 94%
m.p. : 68-70℃
^{1}H NMR($CDCl_3$) δ : 1.13(3H,t), 1.47(3H,d), 2.33(6H,s), 2.44(3H,s),

2.95(4H,t), 3.30(4H,t), 3.98(3H,s), 4.10(2H,q), 5.01(1H,q), 6.46(3H,m), 7.71(1H,s)

Example 169

2-({[4-(3,5-Dimethylphenyl)piperazino]carbonyl}[5-(1-hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]amino)acetic acid:

Ethyl 2-({[4-(3,5-dimethylphenyl)piperazino]carbonyl}[5-(1-hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]amino)acetate was reacted by the same way with the example 165 to obtain the titled compound.

yield : 92%

m.p. : 114-116℃

^{1}H NMR($CDCl_3$) δ : 1.40(3H,d), 2.23(6H,s), 2.40(3H,s), 2.91(4H,t), 3.21(4H,t), 3.98(3H,s), 4.06(2H,s), 4.90(1H,q), 6.50(3H,m), 6.51(1H,s)

Example 170

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-phenylpiperazine

a) 3,4-Dimethyl anisole:

To 3,4-dimethylphenol(19.3g, 0.16mol), methanol(150ml) and KOH(9.65g, 0.25mol) were added and then refluxed for 2hrs. Methyl iodide(36.5g, 0.25mol) was added thereto, refluxed for 3 hours and then followed by addition of water(150ml). The resulting mixture was extracted with ethylacetate and purified by column chromatography to obtain the titled compound.

yield : 81%

^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.24(3H,s), 3.77(3H,s), 6.71(2H,m), 6.97(1H,s)

b) 4,5-Dimethyl-2-nitroanisole:

Trifluoroacetic acid(250ml) was added into 3,4-dimethylanisole(17.1g, 0.13mol), successively sodium nitrite(16.6g, 0.24mol) was added slowly in water bath, and stirred at room temperature for 14 hrs. After trifluoroacetic acid was removed and water was added thereto, the resulting mixture was extracted with ether, and purified by column chromatography to obtain the titled compound.

yield : 55%

^{1}H NMR(500MHz, $CDCl_3$): δ 2.25(3H,s), 2.32(3H,s), 3.94(3H,s),

6.85(1H,s), 7.70(1H,s)

c) 4,5-Dimethyl-2-methoxyaniline:

Tetrahydrofuran(100ml) and ethanol(40ml) were added into 4,5-dimethyl-2-nitroanisole(7.80g, 0.043mol) and then added 10% Pd/activated carbon(0.57g) slowly, hydrogenated for 5 hrs. The reaction was completed by the same way with the above and the resulting product was purified by column chromatography to obtain the titled compound.

yield : 82%

^{1}H NMR(500MHz, $CDCl_3$): δ 2.23(3H,s), 2.27(3H,s), 3.90(3H,s), 6.80(1H,s), 7.68(1H,s)

d) Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate:

To 4,5-dimethyl-2-methoxyaniline(4.50g, 0.03mol), methylene chloride(100ml) was added and phenyl chloroformate(4.80g, 0.03mol) was added slowly. The resulting solution was stirred for 2 hrs and thereto water(150ml) was added, and extracted with methylene chloride and purified by column chromatography to obtain the titled compound.

yield : 98%

^{1}H NMR(500MHz, $CDCl_3$): δ 2.24(3H,s), 2.27(3H,s), 3.89(3H,s), 6.85(1H,s), 7.20(5H,m), 7.90(1H,s)

e) 1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-phenylpiperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate(5.422g, 0.02mol) and 1-phenylpiperazine(3.44g, 0.02mol) were dissolved in tetrahydrofuran(10ml). After DBU(3.04g, 0.02mol) was added, the resulting solution was stirred at room temperature for 2 hrs, concentrated and purified by column chromatography to obtain the titled compound.

yield : 85%

m.p.: 143-144℃

^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.21(3H,s), 3.25(4H,t), 3.67(4H,t), 3.85(3H,s), 6.64(1H,s), 6.94(3H,m), 6.99(1H,s), 7.29(1H,t), 7.91(1H,s)

Example 171

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and

1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield : 85%
m.p. : 119-120℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.21(3H,s), 3.27(4H,t), 3.70(4H,t), 3.79(6H,s), 3.85(3H,s), 6.17(2H,m), 6.65(1H,s), 6.98(1H,s), 7.90(1H,s)
Mass(EI) m/z : Calcd for $C_{22}H_{29}N_3O_4$ 399.2158, found 399.2168

Example 172
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield : 88%
m.p. : 177-178℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.21(3H,s), 2.29(6H,s), 3.23(4H,t), 3.66(4H,t), 3.85(3H,s), 6.58(2H,m), 6.65(1H,s), 6.99(1H,s), 7.92(1H,s)
Mass(EI) m/z : Calcd for $C_{22}H_{29}N_3O_2$ 367.2259, found 367.2290

Example 173
1-[4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2,3-dimethylphenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(2,3-dimethylphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield : 95%
m.p. : 140-142℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.21(3H,s), 2.22(3H,s), 2.27(3H,s), 2.29(3H,s), 2.95(4H,t), 3.67(4H,t), 3.85(3H,s), 6.65(1H,s), 7.01(3H,m), 7.93(1H,s)

Example 174
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2,3,5,6-tetramethylphenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(2,3,5,6-tetramethylphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield : 93%
m.p. : oil phase
^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(9H,s), 2.21(9H,s), 3.17(4H,t), 3.63(4H,t), 3.84(3H,s), 6.64(1H,s), 6.84(1H,s), 7.95(1H,s)

Example 175
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-difluorophenyl) piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield : 89%
m.p. : 102-103℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.22(3H,s), 3.29(4H,t), 3.68(4H,t), 3.85(3H,s), 6.65(1H,s), 6.97(3H,m), 7.89(1H,s)

Example 176
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2-chlorophenyl) piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(2-chlorophenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield : 90%
m.p. : 176-177℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.21(3H,s), 2.22(3H,s), 3.10(4H,t,J=5.0Hz), 3.69(4H,t,J=5.0Hz), 3.85(3H,s), 6.65(1H,s), 7.02(2H,m), 7.24(1H,m), 7.39(1H,d,J=4.0Hz), 7.92(1H,s)

Example 177
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3-chlorophenyl) piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(3-chlorophenyl)piperazine were reacted by the same way with the

example 170 to obtain the titled compound.
yield : 84%
m.p. : 75-76℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.22(3H,s), 3.27(4H,t,J=5.0Hz), 3.68(4H,t,J=5.0Hz), 3.85(3H,s), 6.65(1H,s), 6.90(3H,m), 7.21(1H,t), 7.90(1H,s)
Mass(EI) m/z : Calcd for $C_{20}H_{24}N_3O_2Cl_1$ 373.1557, found 373.1590

Example 178
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2-hydroxyphenyl) piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(2-hydroxyphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield : 87%
m.p. : 197-199℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.21(3H,s), 2.98(4H,t), 3.72(4H,t), 3.84(3H,s), 6.65(1H,s), 6.89(1H,t), 7.00(2H,m), 7.13(2H,m), 7.89(1H,s)

Example 179
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3-hydroxyphenyl) piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(3-hydroxyphenyl) were reacted by the same way with the example 170 to obtain the titled compound.
yield : 88%
m.p. : 177-178℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.19(3H,s), 2.21(3H,s), 3.24(4H,t), 3.68(4H,t), 3.85(3H,s), 6.41(3H,m), 6.65(1H,s), 6.98(1H,s), 7.13(1H,t), 7.88(1H,s)

Example 180
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3-thiophenyl) piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(3-thiophenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

yield: 79%
m.p.: 108-110℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.21(3H,s), 3.26(4H,t), 3.65(4H,t), 3.84(3H,s), 6.64(1H,s), 6.97(4H,m), 7.05(1H,s), 7.89(1H,s)

Example 181
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2-acetoxyphenyl) piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(2-acetoxyphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield: 84%
m.p.: 129-131℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.21(3H,s), 2.32(3H,s), 3.05(4H,t), 3.63(4H,t), 3.85(3H,s), 6.64(1H,s), 6.99(1H,s), 7.04(1H,m), 7.17(2H,m), 7.22(1H,m), 7.90(1H,s)

Example 182
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3-acetoxyphenyl) piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(3-acetoxyphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield: 87%
m.p.: 154-156℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.21(3H,s), 2.29(3H,s), 3.27(4H,t), 3.68(4H,t), 3.85(3H,s), 6.64(1H,s), 6.66(2H,m), 6.82(1H,m), 6.98(1H,s), 7.90(1H,s)

Example 183
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2-methoxyphenyl) piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield: 90%

m.p.: 144-145℃

^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.22(3H,s), 2.26(3H,s), 2.95(4H,t, J=5.0Hz), 3.65(4H,t,J=5.0Hz), 3.78(3H,s), 3.85(3H,s), 6.59(1H,s), 6.65(1H,s), 7.00(1H,s), 7.11(1H,s), 7.93(1H,s)

Example 184

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(5-methoxy-2-methylphenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(5-methoxy-2-methylphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

yield: 88%

m.p.: 140-141℃

^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.22(3H,s), 2.26(3H,s), 2.95(4H,t, J=5.0Hz), 3.65(4H,t,J=5.0Hz), 3.78(3H,s), 3.85(3H,s), 6.59(1H,s), 6.65(1H,s), 7.00(1H,s), 7.11(1H,s), 7.93(1H,s)

Example 185

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2-methoxy-5-methylphenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(2-methoxy-5-methylphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

yield: 80%

m.p.: 107-108℃

^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.21(3H,s), 2.29(3H,s), 3.10(4H,t, J=5.0Hz), 3.69(4H,t,J=5.0Hz), 3.85(3H,s), 3.86(3H,s), 6.55(1H,s), 6.79(2H,m), 7.01(1H,s), 9.94(1H,s)

Example 186

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2-methoxy-5-phenylphenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(2-methoxy-5-phenylphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

yield: 91%

m.p.: 139-140℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.21(3H,s), 2.22(3H,s), 3.20(4H,t), 3.74(4H,t), 3.85(3H,s), 3.94(3H,s), 6.65(1H,s), 7.02(2H,m), 7.32(2H,m), 7.42(2H,t), 7.55(2H,d), 7.93(1H,s)

Example 187
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2-isopropenyl phenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(2-isopropenylphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield: 80%
m.p.: 134-135℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.21(6H,s), 3.10(4H,t), 3.64(4H,t), 3.85(3H,s), 5.08(1H,s), 5.14(1H,s), 6.64(1H,s), 7.05(3H,m), 7.70(1H,m), 7.92(1H,s)

Example 188
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(1-naphthyl) piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(1-naphthyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield: 92%
m.p.: 160-162℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.24(3H,s), 3.31(4H,t,J=5.0Hz), 3.83(3H,s), 4.04(4H,t), 6.39(2H,m), 6.69(1H,s), 7.13(1H,t), 7.30(1H,s), 7.46(1H,s)

Example 189
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(1-anthranyl) piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(1-anthranyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield: 94%

m.p.: 74-75℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.22(3H,s), 3.24(4H,t), 3.70(4H,t), 3.86(3H,s), 6.70(1H,s), 7.05(3H,m), 7.45(5H,m), 8.00(2H,m)

Example 190
1-[N-(4,5-Dimethyl-2-methoxyphenyl)-N-methylaminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
1-[(4,5-dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(0.2g, 0.5mmole) was dissolved in dimethylformamide(15ml), sodium hydride(12mg, 0.5mmole) was added thereto slowly, and then the resulting mixture was stirred at room temperature for 15 min, then followed by addition of iodomethane(71mg, 0.5mmole) and subsequently at room temperature for 16 hours. The resulting mixture was concentrated under the reduced pressure to remove the used solvent, extracted with methylene chloride, dried, filtered and purified by column chromatography to obtain the titled compound.
yield: 92%
m.p.: 86-88℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.21(3H,s), 2.24(3H,s), 2.92(4H,t), 3.06(3H,s), 3.31(4H,t), 3.75(6H,s), 3.83(3H,s), 6.00(3H,m), 6.71(1H,s), 6.83(1H,s)
Mass(EI) m/z : Calcd for $C_{23}H_{31}N_3O_4$ 413.2314, found 413.2293

Example 191
1-[N-(4,5-Dimethyl-2-methoxyphenyl)-N-methylaminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 190 to obtain the titled compound.
yield: 90%
m.p.: 137-138℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.15(3H,s), 2.24(9H,s), 2.88(4H,t), 3.06(3H,s), 3.29(4H,t), 3.83(3H,s), 6.45(3H,m), 6.71(1H,s), 6.83(1H,s)
Mass(EI) m/z : Calcd for $C_{23}H_{29}N_3O_2$ 381.2416, 381.2436

Example 192

1-[N-(4,5-Dimethyl-2-methoxyphenyl)-N-methylaminocarbonyl]-4-(3,5-difluorophenyl)piperazine:

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-difluorophenyl) piperazine was reacted by the same way with the example 190 to obtain the titled compound.

yield: 87%

m.p.: 98-100℃

^{1}H NMR(500MHz, $CDCl_3$): δ 2.16(3H,s), 2.25(3H,s), 2.92(4H,t), 3.06(3H,s), 3.29(4H,t), 3.83(3H,s), 6.23(3H,m), 6.72(1H,s), 6.83(1H,s)

Example 193

1-[N-Ethyl-N-(4,5-dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(0.2g, 0.5mmole) was dissolved in dimethylformamide(15ml), and thereto sodium hydride(12mg, 0.5mmole) was added slowly. The resulting mixture was stirred at room temperature for 15 min. After iodoethane(78mg, 0.5mmol) was added, the resulting mixture was stirred at room temperature for 16 hours. The resulting mixture was concentrated under the reduced pressure to remove the used solvent, extracted with methylene chloride, dryed, filtered and purified by column chromatography to obtain the titled compound.

yield: 89%

m.p.: oil phase

^{1}H NMR(500MHz, $CDCl_3$): δ 1.09(3H,t), 2.16(3H,s), 2.24(3H,s), 2.75(4H,t), 3.28(4H,t), 3.52(2H,q), 3.75(6H,s), 3.81(3H,s), 5.98(3H,m), 6.70(1H,s), 6.80(1H,s)

Example 194

1-[N-(4,5-Dimethyl-2-methoxyphenyl)-N-ethylaminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethyl phenyl)piperazine was reacted by the same way with the example 193 to obtain the titled compound.

yield: 93%

m.p.: 80-82℃
^{1}H NMR(500MHz, $CDCl_3$): δ 1.21(3H,t), 2.15(3H,s), 2.23(9H,s), 2.90(4H,t), 3.25(4H,t), 3.59(2H,q), 3.81(3H,s), 6.45(3H,m), 6.69(1H,s), 6.81(1H,s)

Example 195
1-[N-(4,5-Dimethyl-2-methoxyphenyl)-N-ethylaminocarbonyl]-4-(3,5-difluorophenyl)piperazine:
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-difluorophenyl) piperazine was reacted by the same way with the example 193 to obtain the titled compound.
yield: 87%
m.p.: oil phase
^{1}H NMR(500MHz, $CDCl_3$): δ 1.09(3H,t), 2.16(3H,s), 2.25(3H,s), 2.90(4H,t), 3.27(4H,t), 3.52(2H,q), 3.81(3H,s), 6.24(3H,m), 6.70(1H,s), 6.81(1H,s)

Example 196
1-[N-Isopropyl-N-(4,5-dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-difluorophenyl)piperazine:
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-difluorophenyl) piperazine(0.2g, 0.52mmole) was dissolved in dimethylformamide(15ml) and thereto sodium hydride(12.48mg, 0.52mmole) was slowly added. The resulting mixture was stirred at room temperature for 15 min. After 2-iodopropane(87.88mg, 0.52mmole) was added thereto, the resulting mixture was stirred at room temperature for 16 hours. The resulting mixture was concentrated under the reduced pressure to remove the used solvent, extracted with methylene chloride, dryed, filtered and purified by column chromatography to obtain the titled compound.
yield: 84%
m.p.: oil phase
^{1}H NMR(500MHz, $CDCl_3$): δ 1.10(3H,s), 1.26(3H,s), 2.20(3H,s), 2.25(3H,s), 2.86(4H,t), 3.26(4H,t), 3.77(3H,s), 4.25(1H,m), 6.17(3H,m), 6.68(1H,s), 6.82(1H,s)

Example 197
1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(3,5-dimethoxy phenyl)piperazine:

(a) Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate:
To 3,4-dimethyl-2-methoxyaniline(4.50g, 0.03mol), methylene chloride(100ml) was added and then phenyl chlorothionoformate(5.16g, 0.03mol) was added slowly. The resulting mixture was stirred for 2 hours, and thereto water(150ml) was added. The resulting mixture was extracted with methylene chloride and purified by column chromatography to obtain the titled compound.
yield: 92%
^{1}H NMR(500MHz, $CDCl_3$): δ 2.21(3H,s), 2.25(3H,s), 3.85(3H,s), 6.80(1H,s), 6.93(5H,m), 7.31(1H,s)

(b) 1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate(0.2g, 0.7mmol) and 1-(3,5-dimethoxyphenyl)piperazine(0.16g, 0.7mmol) were dissolved in tetrahydrofuran(10ml) and thereto DBU(0.11g, 0.7mmole) was added, followed by stirring at room temperature for 2 hours. The resulting product was concentrated and purified by chromatography to obtain the titled compound.
yield: 84%
m.p.: 128-129℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.24(3H,s), 2.32(6H,s), 3.37(4H,t), 3.83(3H,s), 4.08(4H,t), 6.69(3H,m), 7.39(1H,m), 7.47(1H,s)
Mass(EI) m/z : Calcd for $C_{22}H_{29}N_3O_3S_1$ 415.1929, found 415.1912

Example 198
1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(3,5-dimethylphenyl)perazine were reacted by the same way with the example 197 to obtain the titled compound.
yield : 90%
m.p.: 164-165℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.24(3H,s), 2.32(6H,s), 3.37(4H,t), 3.83(3H,s), 4.08(4H,t), 6.69(3H,m), 7.39(1H,m), 7.47(1H,s)
Mass(EI) m/z : Calcd for $C_{22}H_{29}N_3O_1S_1$ 383.2031, found 383.2086

Example 199

1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(2,3-dimethylphenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(2,3-dimethylphenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.

yield: 89%

m.p.: 151-152℃

^{1}H NMR(500MHz, $CDCl_3$): δ 2.21(3H,s), 2.24(3H,s), 2.29(6H,s), 3.03(4H,t), 3.83(3H,s), 4.10(4H,t), 6.69(1H,s), 6.97(2H,m), 7.11(1H,t)

Example 200

1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(3,5-difluorophenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.

yield : 92%

m.p.: 167-168℃

^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.24(3H,s), 2.27(3H,s), 2.32(3H,s), 3.39(4H,t,J=5.0Hz), 3.83(3H,s), 4.14(4H,t), 6.70(1H,s), 6.80(2H,m), 7.36(1H,s), 7.44(1H,s)

Example 201

1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(3,5-dichlorophenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.

yield: 85%

m.p.: 188-189℃

^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.24(3H,s), 3.35(4H,t,J=5.0Hz), 3.83(3H,s), 4.04(4H,t,J=5.0Hz), 6.70(2H,m), 6.83(1H,s), 7.30(1H,s), 7.48(1H,s)

Mass(EI) m/z : Calcd for $C_{20}H_{24}N_3O_2Cl_1$ 423.0938, 423.0956

Example 202

1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(2-fluorophenyl) piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(2-fluorophenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.

yield: 87%

m.p.: 139-140℃

^{1}H NMR(500MHz, $CDCl_3$): δ 2.21(3H,s), 2.24(3H,s), 3.40(4H,t), 3.83(3H,s), 4.25(4H,t), 6.70(1H,s), 7.13(3H,m), 7.37(2H,m)

Example 203

1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(2-chlorophenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(2-chlorophenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.

yield: 85%

m.p.: 115-116℃

^{1}H NMR(500MHz, $CDCl_3$): δ 2.21(3H,s), 2.24(3H,s), 3.18(4H,t), 3.83(3H,s), 4.09(4H,t), 6.69(1H,s), 7.05(2H,m), 7.33(1H,s), 7.41(2H,m)

Example 204

1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(2-methoxyphenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.

yield: 90%

m.p.: oil phase

^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.23(3H,s), 3.14(4H,t,J=5.0Hz), 3.82(3H,s), 3.88(3H,s), 4.06(4H,t,J=5.0Hz), 6.69(1H,s), 6.94(3H,m), 7.30(1H,s), 7.40(1H,s)

Example 205

1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-

(2-methylthiophenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(2-methylthiophenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.
yield: 93%
m.p.: 136-137℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.26(3H,s), 2.45(3H,s), 3.33(4H,t), 3.82(3H,s), 4.39(4H,t), 6.74(1H,s), 7.16(3H,m), 7.47(2H,m)

Example 206
1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(3-hydroxyphenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(3-hydroxyphenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.
yield: 77%
m.p.: Decomposed(200℃)
^{1}H NMR(500MHz, $CDCl_3$): δ 2.17(3H,s), 2.23(3H,s), 3.31(4H,t), 3.82(3H,s), 4.03(3H,t), 6.37(2H,m), 6.47(1H,d), 6.69(1H,s), 7.13(1H,t), 7.45(1H,s)

Example 207
1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(2-phenoxyphenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(2-phenoxyphenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.
yield: 86%
m.p.: oil phase
^{1}H NMR(500MHz, $CDCl_3$): δ 2.17(3H,s), 2.24(3H,s), 3.19(4H,t), 3.80(3H,s), 3.85(4H,t), 6.66(1H,s), 6.91(2H,m), 6.98(1H,m), 7.05(3H,m), 7.13(1H,m), 7.23(1H,m), 7.31(2H,m), 7.36(1H,s)

Example 208
1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(2-isopropenylphenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(2-isopropenylphenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.
yield: 75%
m.p.: 157-158℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.21(3H,s), 2.24(3H,s), 3.19(4H,t), 3.82(3H,s), 4.05(4H,t), 5.07(1H,s), 5.16(1H,s), 6.69(1H,s), 7.11(3H,m), 7.33(1H,s), 7.45(1H,s)

Example 209
1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(2-methoxy-5-methylphenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(2-methoxy-5-methylphenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.
yield: 87%
m.p.: oil phase
^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.23(3H,s), 2.29(3H,s), 3.13(4H,t), 3.83(3H,s), 3.85(3H,s), 4.05(4H,t), 6.69(1H,s), 6.83(2H,m), 7.30(1H,s), 7.40(1H,s)

Example 210
1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(1-naphthyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(1-naphthyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.
yield: 87%
m.p.: 139-140℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.23(3H,s), 2.24(3H,s), 3.21(4H,t), 3.84(3H,s), 4.09(4H,t), 6.70(1H,s), 7.10(1H,d), 7.48(5H,m), 7.85(1H,m), 8.22(1H,d)

Example 211
1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-4-methylphenyl)carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield: 91%
m.p.: 103-105℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.54(3H,s), 2.59(3H,s), 3.27(4H,t), 3.70(4H,t), 3.79(6H,s), 3.94(3H,s), 6.13(3H,m), 6.70(1H,s), 7.05(1H,s), 8.72(1H,s)

Example 212
1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminocarbonyl]-4-(3,5-dimethy-lphenyl)piperazine:
Phenyl N-(5-acetyl-2-methoxy-4-methylphenyl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield : 88%
m.p.: 140-142℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.30(3H,s), 2.54(3H,s), 2.59(3H,s), 3.26(4H,t), 3.70(4H,t), 3.97(3H,s), 6.61(3H,m), 6.70(1H,s), 7.06(1H,s), 8.72(1H,s)

Example 213
1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminocarbonyl]-4-(3,5-dichlorophenyl)piperazine:
Phenyl N-(5-acetyl-2-methoxy-4-methylphenyl)carbamate and 1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield: 78%
m.p.: 170-172℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.54(3H,s), 2.59(3H,s), 3.32(4H,t), 3.74(4H,t), 3.94(3H,s), 6.69(1H,s), 6.86(3H,m), 7.04(1H,s), 8.69(1H,s)

Example 214
1-{[5-(1-Hydroxyethyl)-2-methoxy-4-methylphenyl]aminocarbonyl}-4-(3,5-dimethoxyphenyl)piperazine:
1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(0.2g, 0.47mmol) was dissolved in

anhydrous ethanol(15ml), and sodium borohydride(17mg) was added thereto, and then the resulting mixture was stirred at room temperature for 2 hours, concentrated under the reduced pressure to remove ethanol, and purified by column chromatography(ethylacetate:hexane = 1:2) to obtain the titled compound.

yield: 96%

m.p.: 152-154℃

^{1}H NMR(500MHz, $CDCl_3$): δ 1.41(3H,d), 2.32(3H,s), 3.27(4H,t), 3.71(4H,t), 3.79(6H,s), 3.87(3H,s), 5.04(1H,q), 6.10(3H,m), 6.63(1H,s), 7.01(1H,s), 8.22(1H,s)

Example 215

1-{[5-(1-Hydroxyethyl)-2-methoxy-4-methylphenyl]aminocarbonyl}-4-(3,5-dimethylphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 214 to obtain the titled compound.

yield: 96%

m.p.: 140-142℃

^{1}H NMR(500MHz, $CDCl_3$): δ 1.48(3H,d), 2.33(3H,s), 3.26(4H,t), 3.68(4H,t), 3.87(3H,s), 5.06(1H,q), 6.61(3H,m), 6.64(1H,s), 7.01(1H,s), 8.22(1H,s)

Example 216

1-[(2-Methoxy-4-methyl-5-vinylphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-{[5-(1-Hydroxyethyl)-2-methoxy-4-methylphenyl]aminocarbonyl}-4-(3,5-dimethoxyphenyl)piperazine(0.2g, 0.47mmol) was dissolved in chloroform(15ml), pyridium p-toluenesulfonate(0.12g, 0.47mmol) was added thereto, and the resulting mixture was refluxed for 16 hours, and concentrated under the reduced pressure to remove chloroform and purified by column chromatography(ethylacetate:hexane=1:2) to obtain the titled compound.

yield: 84%

m.p.: 163-165℃

^{1}H NMR(500MHz, $CDCl_3$): δ 2.31(3H,s), 3.23(4H,t), 3.58(4H,t), 3.77(6H,s),

3.87(3H,s), 5.20(1H,d), 5.62(1H,d), 6.59(3H,m), 6.63(1H,s), 6.88(1H,t), 6.99(1H,s), 8.32(1H,s)

Example 217

1-[(2-Methoxy-4-methyl-5-vinylphenyl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-{[5-(1-Hydroxyethyl)-2-methoxy-4-methylphenyl]aminocarbonyl}-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 216 to obtain the titled compound.

yield: 82%

m.p.: 201-203℃

^{1}H NMR(500MHz, $CDCl_3$): δ 2.29(6H,s), 2.34(3H,s), 3.24(4H,t), 3.68(4H,t), 3.87(3H,s), 5.22(1H,d), 5.66(1H,d), 6.59(3H,m), 6.63(1H,s), 6.86(1H,t), 7.02(1H,s), 8.32(1H,s)

Example 218

1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-4-methylphenyl)thiocarbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.

yield: 82%

m.p.: 163-165℃

^{1}H NMR(500MHz, $CDCl_3$): δ 2.16(3H,s), 2.56(3H,s), 3.35(4H,t), 3.91(6H,s), 4.03(3H,s), 4.13(4H,t), 6.06(3H,m), 6.73(1H,s), 8.62(1H,s)

Example 219

1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-4-methylphenyl)thiocarbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.

yield: 79%

m.p.: 180-182℃

^{1}H NMR(500MHz, $CDCl_3$): δ 2.29(6H,s), 2.57(6H,s), 3.32(4H,t), 3.92(3H,s), 4.12(4H,t), 6.56(3H,m), 6.72(1H,s), 7.39(1H,s), 8.63(1H,s)

Example 220

1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminothiocarbonyl]-4-(3,5-dichlorophenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-4-methylphenyl)thiocarbamate and 1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.

yield: 79%

m.p.: 201-203℃

^{1}H NMR(500MHz, $CDCl_3$): δ 2.20(3H,s), 2.57(3H,s), 3.46(4H,t), 3.92(3H,s), 4.25(4H,t), 6.64(1H,s), 6.88(3H,m), 7.72(1H,s), 8.57(1H,s)

Example 221

1-{[5-(1-Hydroxyethyl)-2-methoxy-4-methylphenyl]aminothiocarbonyl}-4-(3,5-dimethoxyphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminothiocarbony]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 214 to obtain the titled compound.

yield: 94%

m.p.: 146-148℃

^{1}H NMR(500MHz, $CDCl_3$): δ 1.44(3H,d), 2.32(3H,s), 3.35(4H,t), 3.78(6H,s), 3.84(3H,s), 4.11(4H,t), 5.06(1H,q), 6.13(3H,m), 6.66(1H,s), 7.41(1H,s), 7.77(1H,s)

Example 222

1-{[5-(1-Hydroxyethyl)-2-methoxy-4-methylphenyl]aminothiocarbonyl}-4-(3,5-dimethylphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminothiocarbony]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 214 to obtain the titled compound.

yield: 93%

m.p.: 150-152℃

^{1}H NMR(500MHz, $CDCl_3$): δ 1.44(3H,d), 2.29(6H,s), 2.32(3H,s), 3.30(4H,t), 3.84(3H,s), 4.07(4H,t), 5.06(1H,q), 6.61(3H,m), 6.66(1H,s), 7.38(1H,s), 7.79(1H,s)

Example 223

1-{[5-(1-Hydroxyethyl)-2-methoxy-4-methylphenyl]aminothiocarbonyl}-4-(3,5-dichlorophenyl)piperazine:

1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminothiocarbony]-4-(3,5-dichlorophenyl)piperazine was reacted by the same way with the example 214 to obtain the titled compound.

yield: 77%

m.p.: 166-168℃

^{1}H NMR(500MHz, $CDCl_3$): δ 1.45(3H,d), 2.33(3H,s), 3.35(4H,t), 3.84(3H,s), 4.03(4H,t), 5.07(1H,q), 6.68(3H,m), 6.83(1H,s), 7.37(1H,s), 7.82(1H,s)

Example 224

Ethyl 2-({[4-(3,5-dimethoxyphenyl)piperazino]carbonyl}-2-methoxy-4,5-dimethylanilino)acetate :

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethoxy phenyl)piperazine(0.2g, 0.5mmol) was dissolved in dimethylformamide(15ml), sodium hydride(18.5mg, 0.5mmol) was added thereto, and the resulting mixture was stirred at room temperature. Then, ethyl bromoacetate(83.5mg, 0.5mmol) was added thereto and the resulting mixture was stirred for 3 hours, concentrated under the reduced pressure to remove the used solvent and purified by column chromatography(ethylacetate:hexane=1:2) to obtain the titled compound.

yield: 79%

m.p.: oil phase

^{1}H NMR(500MHz, $CDCl_3$): δ 1.36(3H,t), 2.15(3H,s), 2.23(3H,s), 2.91(4H,t), 3.22(4H,t), 3.82(6H,s), 4.12(3H,s), 4.18(2H,s), 5.98(3H,m), 6.69(1H,s), 7.03(1H,s)

Example 225

Ethyl 2-({[4-(3,5-dimethylphenyl)piperazino]carbonyl}-2-methoxy-4,5-dimethylanilino)acetate :

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 224 to obtain the titled compound.

yield: 78%

m.p.: oil phase

^{1}H NMR(500MHz, $CDCl_3$): δ 1.26(3H,t), 1.56(6H,s), 2.17(3H,s), 2.24(3H,s), 3.32(4H,t), 3.52(4H,t), 3.82(3H,s), 4.15(2H,q), 4.18(2H,s), 6.70(3H,m), 6.94(1H,s), 7.46(1H,s)

Example 226

2-({[4-(3,5-Dimethoxyphenyl)piperazino]carbonyl}-2-methoxy-4,5-dimethylanilino)acetic acid:

Ethyl 2-({[4-(3,5-dimethoxyphenyl)piperazino]carbonyl}-2-methoxy-4,5-dimethylanilino)acetate(200mg, 0.41mmole) was dissolved in dioxane:distilled water(4:1, 15ml), lithium hydroxide monohydrate(50.7mg, 1.23mmol) was added thereto, and then the resulting mixture was stirred at room temperature for 3 hours, acidified with 1N-hydrochloric acid, extracted with ethylacetate, filtered to dryness, concentrated under the reduced pressure to remove the used solvent, and purified by column chromatography(ethylacetate:hexane=1:2) to obtain the titled compound.

yield: 80%

m.p.: 188-189℃

^{1}H NMR(500MHz, $CDCl_3$): δ 2.14(3H,s), 2.23(3H,s), 2.93(4H,t), 3.35(4H,t), 3.75(6H,s), 3.87(3H,s), 4.18(2H,s), 5.96(3H,m), 6.71(1H,s), 7.71(1H,s)

Example 227

2-({[4-(3,5-Dimethylphenyl)piperazino]carbonyl}-2-methoxy-4,5-dimethylanilino)acetic acid:

Ethyl 2-({[4-(3,5-dimethylphenyl)piperazino]carbonyl}-2-methoxy-4,5-dimethylanilino)acetate was reacted by the same way with the example 226 to obtain the titled compound.

yield: 78%

m.p.: 170-171℃

^{1}H NMR(500MHz, $CDCl_3$): δ 2.13(3H,s), 2.24(9H,s), 2.91(4H,t), 3.35(4H,t), 3.83(3H,s), 4.18(2H,s), 6.45(3H,m), 6.70(2H,s), 6.80(1H,s)

Example 228

1-[(2-Hydroxy-4,5-dimethylphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

(a) 4,5-Dimethyl-2-nitrophenol:
To 3,4-dimethylphenol(12.1g, 0.1mol), trifluoroacetic acid(250ml) was added, and in water bath sodium nitrite(12.4g, 0.18mol) was added slowly. The resulting mixture was stirred at room temperature for 14 hours and concentrated under the reduced pressure to remove trifluoroacetic acid, followed by addition of water(150ml), extracted with ether and purified by column chromatography to obtain the titled compound.
yield: 80%
^{1}H NMR(500MHz, $CDCl_3$): δ 2.23(3H,s), 2.29(3H,s), 6.93(1H,s), 7.84(1H,s)

(b) 4,5-Dimethyl-2-hydroxyaniline:
To 4,5-dimethyl-2-nitrophenol(11.7g, 0.07mol), tetrahydrofuran(100ml) and ethanol(40ml) were added, and 10% palladium/activated carbon(0.57g) was added slowly, and then the mixture was hydrogenated for 5 hours. The reaction mixture was concentrated and chromatographed by the same way above to obtain the titled compound.
yield : 77%
^{1}H NMR(500MHz, $CDCl_3$): δ 2.11(6H,s), 6.56(2H,s)

(c) Phenyl N-(4,5-dimethyl-2-hydroxyphenyl)carbamate:
To 4,5-dimethyl-2-hydroxyaniline(6.80g, 0.05mole), methylene chloride(100ml) was added and then phenyl chloroformate(8.0g, 0.05mole) was added slowly. After stirring for 2 hours, addition of water(150ml), extraction with methylene chloride and column chromatography gave the titled compound.
yield: 92%
^{1}H NMR(500MHz, $CDCl_3$): δ 2.17(6H,s), 6.74(1H,s), 7.15(5H,m), 7.31(1H,s)

(d) Phenyl N-[2-(t-butyldimethylsilyloxy)-4,5-dimethylphenyl]carbamate:
To a mixture of phenyl N-(4,5-dimethyl-2-hydroxyphenyl)carbamate (7.72g, 0.03mol) and imidazole(2.2g, 33mmol), methylene chloride(100ml) was added, and with stirring t-butyldimethylsilylchloride(5.0g, 33mmole)

was added. Then the mixture was stirred for 2 hours, and water(150ml) was added thereto. The resulting mixture was extracted with methylene chloride, dried, concentrated under the reduced pressure and purified by column chromatography to obtain the titled compound.
yield: 83%
^{1}H NMR(500MHz, $CDCl_3$): δ 0.27(6H,s), 0.98(9H,s), 2.17(6H,s), 7.12(5H,m), 7.30(2H,s)

(e) 1-[(2-Hydroxy-4,5-dimethylphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
Phenyl N-[2-(t-butyldimethylsilyloxy)-4,5-dimethylphenyl]carbamate (0.17g, 0.5mmole) and 1-(3,5-dimethoxyphenyl)piperazine(0.13g, 0.6mmole) were dissolved in tetrahydrofuran(10ml), and thereto with stirring DBU(0.09g, 0.6mmole) was added, and the resulting mixture was stirred for 2 hours, concentrated and chromatographed to obtain the titled compound.
yield: 87%
m.p.: 145-146℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.14(3H,s), 2.18(3H,s), 3.26(4H,t), 3.67(4H,t), 3.79(6H,s), 6.07(3H,m), 6.40(3H,m), 6.67(1H,s), 6.82(1H,s), 8.87(1H,s)

Example 229
1-[(2-Hydroxy-4,5-dimethylphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
Phenyl N-[2-hydroxy-4,5-dimethylphenyl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 228 to obtain the titled compound.
yield: 84%
m.p.: 160-162℃
^{1}H NMR(500MHz, $CDCl_3$): δ 2.13(3H,s), 2.17(3H,s), 2.31(6H,s), 3.26(4H,t), 3.75(4H,t), 6.73(3H,m), 6.81(1H,s), 8.86(1H,s)

Example 230
1-[(2-Hydroxy-4,5-dimethylphenyl)aminocarbonyl]-4-(3,5-difluorophenyl) piperazine:
Phenyl N-[2-hydroxy-4,5-dimethylphenyl)carbamate and

1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 228 to obtain the titled compound.

yield: 80%

m.p.: 152-154℃

^{1}H NMR(500MHz, $CDCl_3$): δ 2.17(3H,s), 2.20(3H,s), 3.30(4H,t), 3.70(4H,t), 6.40(3H,m), 6.70(1H,s), 6.82(1H,s), 6.98(1H,s)

Example 231

1-[(2-hydroxy-4,5-dimethylphenyl)aminocarbonyl]-4-(3,5-dichlorophenyl) piperazine:

Phenyl N-(2-hydroxy-4,5-dimethylphenyl)carbamate and 1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 228 to obtain the titled compound.

yield: 77%

m.p.: oil phase

^{1}H NMR(500MHz, $CDCl_3$): δ 2.15(3H,s), 2.20(3H,s), 3.32(4H,t), 3.69(4H,t), 6.29(3H,m), 6.69(1H,s), 6.81(1H,s), 8.65(1H,s)

Antitumor activities of compounds of the present invention were tested in vitro against 5 kinds of human tumor cell lines and 2 kinds of leukemia tumor cell lines. The method and result of in vitro tests is as follows.

Experimental 1 : In vitro antitumor effect against human tumor cell lines.

A. Tumor cell line : A549 (human non-small lung cell)
SKOV-3 (human ovarian)
HCT-15 (human colon)
XF 498 (human CNS)
SKMEL-2 (human melanoma)

B. SRB Assay Method.

a. Human solid tumor cell lines, A549(non-small lung cell), SKMEL-2(melanoma), HCT-15(colon), SKOV-3(ovarian), XF-498(CNS) were cultured at 37℃, in 5% CO_2 incubators using the RPMI 1640 media containing 10% FBS, while they were transfer-cultured successively once or twice per week. Cell cultures were dissolved in a solution of 0.25% trypsin and 3 mM CDTA PBS(-) and then cells were separated from media which the cells were sticked on.

b. $5\times10^3\sim2\times10^4$ cells were added into each well of 96-well plate and cultured in 5% CO_2 incubator, at 37℃, for 24 hours.

c. Each sample drug was dissolved in a little DMSO and diluted with the used medium to a prescribed concentration for experiments, wherein the final concentration of DMSO was controlled below 0.5%.

d. Medium of each well cultured for 24 hours as above b. was removed by aspiration. Each 200 μl of drug samples prepared in c. was added into each well and the wells were cultured for 48 hours. Tz(time zero) plates were collected at the point of time drugs were added.

e. According to the SRB assay method, cell fixing with TCA, staining with 0.4% SRB solution, washing with 1% acetic acid and elution of dye with 10mM Tris solution were carried out on Tz plates and culture-ended plates, and then, OD values were measured at 520 nm.

C. Calculation of result

a. Time zero(Tz) value was determined with measuring the SRB protein value at the point of time drugs were added.

b. Control value(C) was determined with the OD value of an well untreated with drug.

c. Drug-treated test value(T) was determined with the OD value of drug-treated well.

d. Effects of drugs were estimated with growth stimulation, net growth inhibition, net killing etc. calculated from Tz, C and T.

e. If $T \geq Tz$, cellular response function was calculated by $100x(T-Tz)/(C-Tz)$, and if $T < Tz$, by $100\times(T-Tz)/Tz$. The results are shown in the next table 1.

* REFERENCE

1) P. Skehan, R. Strong, D Scudiero, A. Monks, J. B. Mcmahan, D. T. Vistica, J. Warren, H. Bokesh, S. Kenny and M. R. Boyd : Proc. Am. Assoc. Cancer Res., 30, 612(1989)

2) L. V. Rubinstein, R. H. Shoemaker, K. D. Paull, R. M. simon, S. Tosini, P. Skehan, D. Scudiero, A. Monks and M. R. boyd. ; J. Natl. Cancer Inst., 82, 1113(1990)

3) P. Skehan, R. Strong, D. Scudiero, A. monks, J. B. Mcmahan, D. T. Vistica, J. Warren, H. Bokesh, S. Kenny and M. R. Boyd.;J, Natl. Cancer Ins., 82, 1107(1990)

D. Results.

It was found that compounds of the present invention have the

superior antitumor activities than those of cisplatin, one control, and equal to or higher antitumor activities than those of adriamycin, another control, against human solid cancer cell lines.

Table 1. $ED_{50}=\mu g/ml$

Ex. No.	A549	SK-OV-3	SK-MEL-2	XF-498	HCT 15
4	0.007	0.022	0.007	0.94	0.093
5	0.71	0.96	0.60	>10.0	0.96
9	0.15	0.07	0.21	0.11	0.11
11	0.91	0.56	0.62	0.73	0.71
14	0.022	0.02	0.001	0.16	0.007
15	0.002	0.05	0.052	0.035	0.038
16	0.008	0.04	0.038	0.005	0.061
17	0.018	0.01	0.021	0.077	0.008
22	0.0009	0.006	0.027	0.0053	0.01
23	0.09	0.04	0.09	0.092	0.05
24	0.03	0.006	0.01	0.234	0.01
27	0.02	0.11	0.01	0.046	0.165
28	0.06	0.07	0.001	0.41	0.05
46	0.21	0.12	0.08	0.14	0.16
47	0.92	0.62	0.47	0.64	0.81
53	0.47	0.47	0.64	0.67	0.71
56	0.017	0.0027	0.01	0.013	0.045
57	0.27	0.15	0.18	0.22	0.25
63	0.04	0.1	0.11	0.03	0.07
64	0.42	0.56	0.52	0.23	0.37
73	0.01	0.0054	0.02	0.013	0.012
74	0.016	0.0138	0.02	0.026	0.021
75	0.19	0.09	0.09	0.13	0.12

Ex. No.	A549	SK-OV-3	SK-MEL-2	XF 498	HCT 15
81	0.0032	0.0007	0.0107	0.0097	0.0054
82	0.0676	0.0249	0.0754	0.0479	0.0346
85	0.048	0.117	0.039	0.104	0.10
88	0.014	0.043	0.02	0.009	0.011
99	0.43	0.41	0.40	0.52	0.36
100	4.54	3.02	3.47	0.66	4.21
103	0.52	0.46	0.49	0.36	0.33
109	0.47	0.91	0.86	0.53	0.49
110	0.52	1.06	0.97	0.81	0.69
112	0.56	6.43	0.22	2.07	0.61
128	0.40	0.37	0.42	0.44	0.51
132	0.03	0.01	0.03	0.04	0.04
133	0.57	0.94	0.53	0.61	0.57
134	0.0009	0.0091	0.0086	0.002	0.0065
135	0.056	0.092	0.102	0.06	0.066
140	0.33	0.47	0.56	0.54	0.49
142	0.015	0.011	0.021	0.026	0.017
143	0.0004	0.0095	0.0121	0.0009	0.0108
147	0.031	0.092	0.024	0.466	0.18
148	0.01	0.07	0.03	0.05	0.05
151	0.004	0.008	0.007	0.007	0.037
152	0.18	0.37	0.2	0.26	0.44
156	0.06	0.10	0.09	0.06	0.07
157	0.000002	0.000002	0.000043	0.000245	0.000211
159	0.05	0.10	0.07	0.21	0.17

Ex. No.	A549	SK-OV-3	SK-MEL-2	XF 498	HCT 15
171	0.000645	0.00372	0.003233	0.000572	0.001809
172	0.0047	0.0097	0.0233	0.0086	0.0180
174	0.54	0.56	0.27	0.49	0.33
177	0.52	0.39	0.17	0.12	0.09
179	1.04	0.98	0.72	0.74	0.63
183	0.42	2.27	1.17	1.41	2.09
184	0.28	0.34	0.17	0.12	0.20
190	0.004	0.008	0.002	0.443	0.017
191	0.09	0.28	0.06	0.47	0.40
198	0.021	0.068	0.008	0.072	0.56
200	0.50	0.53	0.26	1.01	0.44
201	0.014	0.053	0.049	0.026	0.071
202	0.57	1.26	0.48	2.09	0.64
206	0.47	0.54	0.52	0.70	0.38
Cisplatin	0.8184	0.7134	0.7147	0.7771	3.0381
Adriamycin	0.0168	0.0176	0.0108	0.0250	1.6689

Experimental 2.

In vitro antitumor effects against animal leukemia cells.

A. Materials :

Tumor cell lines : L1210(mouse leukemia cell)
P388 (mouse lymphoid neoplasma cell)

B. Method : Dye Exclusion Assay.

1) The concentrations of L1210 and P388 cells being cultured in RPMI 1640 media containing 10% FBS were regulated to 1×10^6 cells/ml.

2) Sample drugs of respective concentrations diluted in the ratio of log doses were added into cell media, and cultured at 37℃, for 48 hours, in 50% CO_2 incubator, and then viable cell number was measured by dye exclusion test using trypan blue.

3) The concentration of sample compounds showing 50 % cell growth inhibition(IC_{50}) compared with the control were determined and listed in the table 2 below.

* REFERENCE

1) P. Skehan, R. Strong, D. Scudiero, A. Monks, J. B. Mcmahan, D. T. Vistica, J. Warren, H. Bokesh, S. Kenney and M. R. Boyd. : Proc. Am. Assoc. Cancer Res., 30, 612(1989).

2) L. V. Rubinstein, R. H. Shoemaker, K. D. Paull, R. M. Simon, S. Tosini, P. Skehan, D. Scudiero, A. Monks, J. Natl. Cancer Inst., 82, 1113(1990)

3) P. Skehan, R. Strong, D. Scudiero, J. B. Mcmahan, D. T. Vistica, J. Warren, H. Bokesch, S. Kenney and M. R. Boyd. : J. Natl. Cancer Inst., 82, 1107(1990)

C. Results

As the results of measurement of antitumor activities of compounds of the present invention against L1210 and P388 mouse cancer cells, it was found that the compounds tested have equal to or higher antitumor activities than those of the control drug, mitomycin C.

Ex. No.	L1210	P388
8	0.9	0.4
12	0.2	-
13	0.5	-
14	0.3	-
15	0.3	0.4
16	0.5	0.3
17	1.2	0.8
24	0.5	0.5
49	1.5	-
56	0.2	0.2
57	1.8	1.2
60	1.1	-
63	0.5	0.3
64	1.9	1.4
69	-	0.5
71	-	0.07
72	-	0.9
73	0.2	0.04
74	0.5	0.4
76	-	0.4
77	-	0.5

Ex. No.	L1210	P388
132	0.4	0.4
134	0.5	0.2
140	1.8	1.6
143	0.5	0.4
144	1.2	0.5
148	1.6	-
149	1.0	0.6
151	-	1.2
152	0.3	0.3
154	-	0.1
157	1.7	1.0
158	0.5	0.2
170	0.4	0.4
173	0.5	0.2
178	1.8	1.6
181	0.5	0.4
182	1.2	0.5
186	1.6	-
187	1.0	0.6
190	0.3	0.3
195	1.7	1.0
196	0.5	0.2
Mitomycin	1.6	1.1

Experimental 3.

In vivo antitumor effects against mouse leukemia P388 cells.

A. Material of experiment

BDF1 mice were used.

B. Method of experiment

1) Leukemia P388 cells being transfer-cultured successively in DBA/2 mouse, were grafted into each mouse of a group comprising 8 mice of 6 week old BDF1 mouse with the dose of 1×10^6cells/0.1ml.

2) Sample drugs were dissolved in PBS or suspended in 0.5% tween 80, and then injected into abdominal cavity of mouse at each prescribed concentration on days 1, 5, 9, respectively.

3) With observation everyday, survival times of tested mice were measured. Antitumor activities was determined in such a manner that the increasing ratio(T/C%) of average survival days of drug-treated groups compared with the control group was calculated using the mean survival times of each tested groups.

The results are shown at the next table 3.

Ex. No.	Dose(mg/kg)	T/C(%)	Interval of administration
8	200 100	140.9 104.5	on days 1, 5, 9
15	25 10	150 110	nine everyday
16	50 25	165 110	nine everyday
22	100 50 25	150 140 110	nine everyday
56	200 100 50	227.3 140.9 118.2	on days 1, 5, 9
56	50 25 10	165.0 145.0 140.0	nine everyday
73	50 25 10	180.0 150.0 140.0	nine everyday
74	50 25 10	250.0 150.0 140.0	nine everyday

Ex. No.	Dose(mg/kg)	T/C(%)	Interval of adminstration
81	200 100 50	218.2 145.5 127.3	on day 1, 5, 9
81	50 25 10	210.0 140.0 140.0	nine everyday
82	100 50	127.3 100.0	on days 1, 5, 9
98	100 50 25	150.0 110.0 110.0	nine everyday
135	100 50 25	150.0 110.0 100.0	nine everyday
144	200 100 50	125.0 110.0 110.0	nine everyday
171	100 50 25	140.0 100.0 100.0	on days 1, 4, 8
172	200 100 50	190.9 127.3 118.2	on days 1, 4, 8

* REFERENCE

A. Goldin et al.: Euro. J. Cancer, 17, 129 (1981).

C. Result

Through in vivo experiments using P388 mouse cancer cells, significant antitumor effect of the compounds of examples were observed.

Experimental 4.

Acute toxicity test (LD_{50}) : Litchfield-Wilcoxon method.

6 weeks old ICR mice(male 30±2.0g) were fed freely with solid feed and water at room temperature, 23±1℃ and at humidity 60±5%. Sample drugs were injected into the abdominal cavities of mice, while each group comprises 6 mice. Observed during 14 days, external appearances and life or dead were recorded, and then, visible pathogenies were observed from dead animals by dissection. LD_{50} value was calculated by Litchfiled-wilcoxon method.

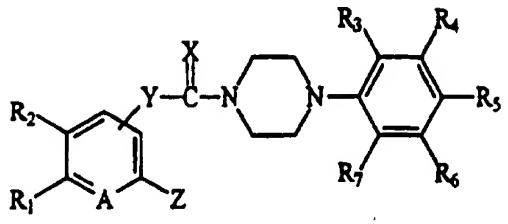
The results are shown at the next table 4.

Ex. No.	LD_{50}(mg/kg)(i.p)
8	707
12	165
13	284.8
15	190
16	282.8
22	>2,000
28	>2,000
56	410
57	455
73	250
74	361.4
81	1,600
82	700
170	573
172	723
182	348
184	309
186	>2,000
187	417.6
Cisplatin	9.7

As described above, it was found that the compounds of the present invention are more safer and have superior antitumor activities to cisplatin, and accordingly have solved the problems of drugs by the prior art such as restriction of dosage, toxicity, tc.

What is claimed:

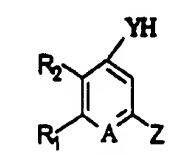
1. A compound of the general formula(I)



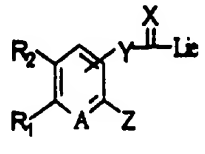
(I)

wherein R_1 and R_2 are independently hydrogen, substituted or unsubstituted C_1-C_8 alkyl, substituted or unsubstituted C_3-C_6 cycloalkyl, substituted or unsubstituted C_2-C_8 unsaturated alkyl, ketone, substituted or unsubstituted aryl, substituted or unsubstituted C_1-C_4 alkoxy, substituted or unsubstituted arylhydroxy, substituted or unsubstituted amino, C_1-C_4 lower ester, C_1-C_4 lower thioester, thiol, substituted or unsubstituted carboxyl, epoxy, substituted or unsubstituted C_1-C_4 lower thioalkoxy; or R_1 and R_2 are fused to form C_3-C_4 saturated or unsaturated chain; R_3, R_4, R_5, R_6 and R_7 are independently hydrogen, halogen, hydroxy, nitro, C_1-C_4 lower ester, C_1-C_4 lower alkyl, C_1-C_4 lower thioalkyl, substituted or unsubstituted C_3-C_6 cycloalkyl, C_1-C_4 lower alkoxy, C_1-C_4 lower thioalkoxy, substituted or unsubstituted aryl, substituted or unsubstituted lower arylalkoxy, substituted or unsubstituted lower alkylamino, or lower alkyl substituted or unsubstituted carbamate; or among R_3, R_4, R_5, R_6 and R_7, two adjacent groups are bonded with each other to form 1,2-phenylene or 2,3-naphthylene; X is oxygen, sulfur, or substituted or unsubstituted imino; Y is bonded at the 3-position or 4-position of the aromatic ring part wherein Y is oxygen or $-NR_8-$ (wherein, R_8 is the same with the above-mentioned R_3.); Z is hydroxy, C_1-C_4 lower alkoxy, C_1-C_4 lower thioalkoxy, substituted or unsubstituted aryloxy, C_1-C_4 lower alkylamino, substituted or unsubstituted cycloamino containing 1-5 nitrogen atoms; A is nitrogen or -CH=; and pharmaceutically acceptable acid addition salts thereof.

2. A process for the preparation of compound of the general formula(I) or a pharmaceutically acceptable acid addition salt thereof comprising reacting a compound of the general formula(a) with a -C(=X)- group-providing agent in the presence of organic solvent to obtain a compound of the general formula(b) and reacting the compound of the general formula(b) with a compound of the general formula(c).



(a)



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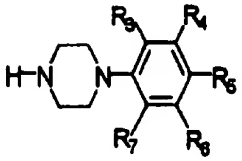
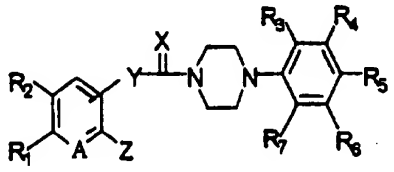


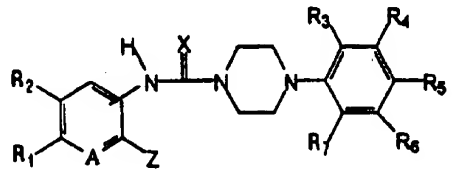
(c)



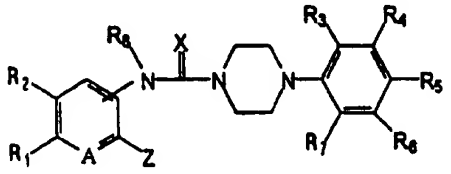
(I)

wherein, R_1, R_2, R_3, R_4, R_5, R_6, R_7, A, X, Y and Z are as defined above and Lie is a leaving group .

3. A process for the preparation of compound of the general formual(Ib) by introducing R_8 providing agent into a compound of the general formula(Ia).



(Ia)



(Ib)

wherein, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, A, X and Z are as defined above.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 97/00128

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 D 213/65, 213/68, 295/108, 295/13, 409/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: C 07 D 213/00, 295/00, 409/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT; Chem. Abstr.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Questel: DARC, CAS; EPO: WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	Chemical Abstracts, Vol.110, No.4, 23 January 1989 (Columbus, Ohio, USA), page 499, column 1, abstract No.31325d, YOSHIMOTO, S. et al.:"Silver halide photographic material giving stable magenta color images", & Jpn. Kokai Tokkyo Koho JP 63,115,167 [88,115,167].	1-3
A	US 5 461 047 A (HANSEN) 24 October 1995 (24.10.95), claims; example 43.	1-3
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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 September 1997 (03.09.97)	05 September 1997 (05.09.97)

Name and mailing address of the ISA/AT	Authorized officer
AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna	Hammer
Facsimile No. 1/53424/535	Telephone No. 1/53424/374

Form PCT/ISA/210 (second sheet) (July 1992)

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Internati nal application N .
PCT/KR 97/00128

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PCT/KR 97/00128

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